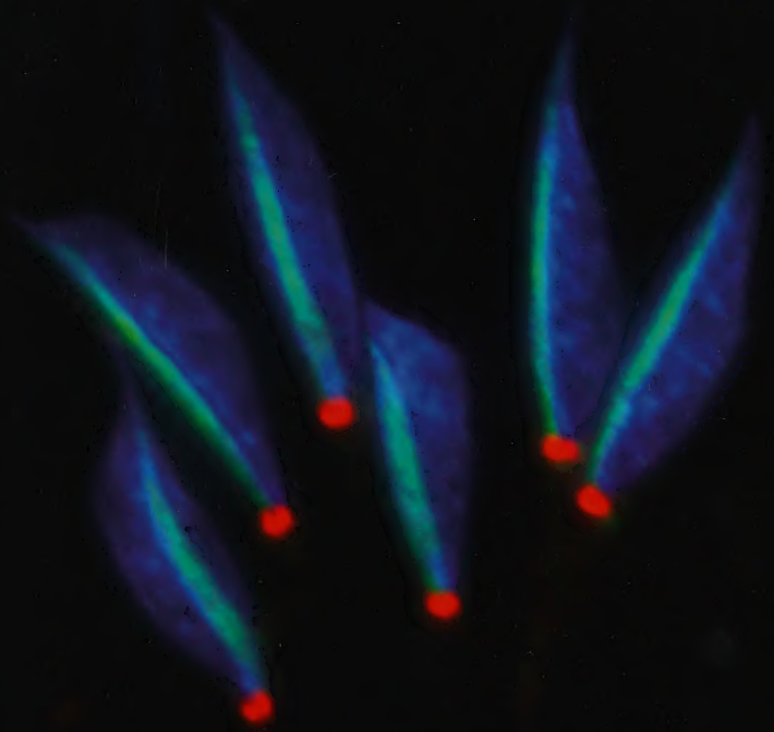
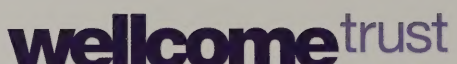
The Wellcome Trust and Cancer Research UK Gurdon Institute

2006 PROSPECTUS / ANNUAL REPORT 2005



Gurdon
INSTITUTE



PROSPECTUS 2006

ANNUAL REPORT 2005

Gurdon INSTITUTE

http://www.gurdon.cam.ac.uk

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CHAIRMAN'S INTRODUCTION

This has been another eventful and successful year for the Gurdon Institute. Most significantly, perhaps, we have now moved into our new building, less than 100 yards away from the original 'Wellcome/CRC' building and on the other side of the Biochemistry Department. The move went smoothly, and although we had some difficulties at the beginning with, for example, the temperature and the lifts, these problems have almost been resolved and we can enjoy working in state-of-the-art accommodation.

Professors Jim Smith and Tony Minson, and Professor Sir John Gurdon look on as Professor Sir Aaron Klug formally opens the new Gurdon Institute. (Philip Mynott, 2005)

To celebrate the move, and the renaming of the Institute that took place on John Gurdon's retirement as Chairman, we held a Symposium at which leading experts in cell, developmental and cancer biology discussed their latest work. The meeting was a great success, and we were particularly pleased and honoured that Professor Sir Aaron Klug, FRS, OM, former Director of the MRC Laboratory of Molecular Biology in Cambridge, Nobel Laureate, and former President of the Royal Society, agreed to conduct the formal opening (see photograph above). We were also delighted that shortly before the Symposium, the Chancellor of the University, the Duke of Edinburgh, visited the Institute to learn about our research; in the photograph opposite Andrea Brand describes asymmetric cell division in *Drosophila* neuroblasts.

The success of the Institute depends on the core support provided by the Wellcome Trust and Cancer Research UK. We were very pleased that both charities agreed to renew our core funding in 2005. We remain enormously grateful for this support, and thank the Trust and CR-UK for their confidence in our work.

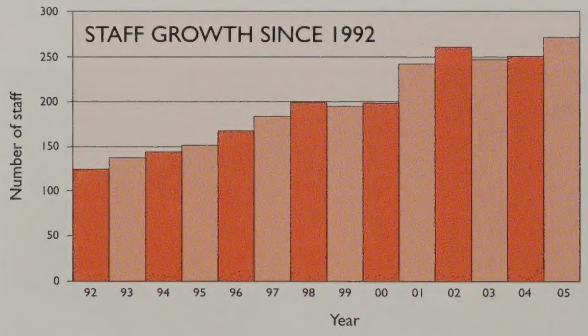
Last year I mentioned the arrival of Eric Miska as a new group leader. Eric has settled in well, and has started all of us thinking about how microRNAs might be relevant to our research. This year I am pleased to report that Masanori Mishima has joined us from the Institute of Molecular Pathology in Vienna. Masanori uses *C elegans* embryos and mammalian cells in culture to study the molecular basis of cytokinesis. In particular, he is interested in how the central spindle and midbody are assembled and how the central spindle/midbody contributes to the progression of cytokinesis.

HRH The Duke of Edinburgh, the Chancellor of the University, on a recent tour of the new Institute (Nigel Luckhurst, 2005)

Research in the Institute, and indeed throughout Cambridge, thrives on interactions between different researchers. To promote such interactions, members of the Gurdon Institute founded the Friday lunchtime Developmental Biology lectures, which we still coordinate, as well as the Cambridge *Drosophila* seminar series. More recently, Rick Livesey has instituted the monthly Developmental Neurobiology Seminar Series, which is open throughout the University, and offers an opportunity for postdoctoral workers and PhD students to present

their work, and Masanori Mishima has started a local Cell Division discussion group. Initiatives such as these ensure that our colleagues gain as much as possible from working in the Institute and from working in the University of Cambridge. It is with the same intention that the Group Leaders spend two days away from Cambridge on 'retreat'. The last retreat was held in November 2005; the next will be early in 2007.

Within the Institute, we are delighted that our colleague Andrea Brand has been made a Senior Group Leader and that other Group Leaders have received national and international honours. Among these, we congratulate Daniel St Johnston, who was elected to Fellowship of the



Royal Society and the Academy of Medical Sciences, and Jon Pines who was elected to the Academy of Medical Sciences.

Amongst other achievements, Andrea Brand shared the William Bate Hardy Prize for the 'best original memoir, investigation or discovery by a member of the University of Cambridge in connection with the Biological Sciences' and John Gurdon was elected to the Charles M and Martha Hitchcock Visiting Professorship at the University of California, Berkeley. Julie Ahringer delivered the 2004 Royal Society Francis Crick Prize lecture.

Azim Surani has been appointed to the Sir Dorabji Tata Visiting Professorship at the Tata Institute of Fundamental Research in India for five years, and with colleagues at the Babraham Institute he has established CellCentric Ltd, which aims to develop novel therapies for cancer and degenerative diseases using products based on molecules that regulate cell fate decisions during early development.

The Institute's students have also had a good year, sweeping the board at the joint meeting of the British Society for Cell Biology and the British Society for Developmental Biology with Eliana Lucas (Jordan Raff's lab) winning the BSCB poster prize and Katja Dahlgaard (Daniel St Johnston's lab) the BSDB award.

Finally, we congratulate Enrique Amaya, who was recently appointed Professor of Tissue Regeneration at the University of Manchester. In his new post Enrique will head a £10 million partnership between the Healing Foundation and the University of Manchester. The newly established Healing Foundation Centre provides space for up to sixty research scientists investigating the cellular and molecular basis of wound healing and tissue regeneration in several model organisms. We will all be very sorry to say farewell to Enrique, who has been at the Institute for nearly 10 years, but we are pleased that he plans to keep lab space here for some time while he gets his lab going in Manchester.

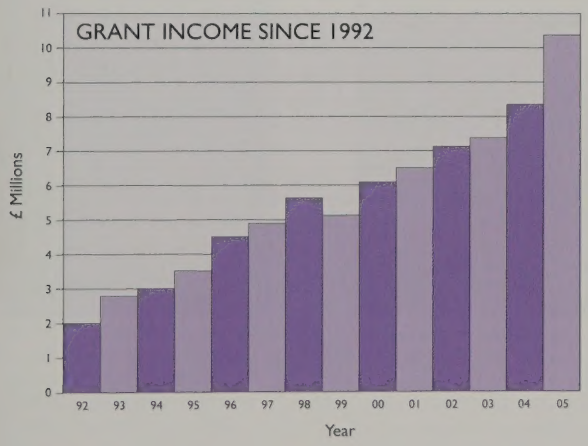
HISTORICAL BACKGROUND

The Institute is situated in the middle of the area containing the science departments of the University of Cambridge and within a short distance of the centre of the historic city. Founded in 1989 to promote research in the areas of developmental biology and cancer biology, the Institute is an assemblage of independent research groups located in one building designed to promote as much interaction as possible. Developmental and cancer biology are complementary since developmental biology is concerned with how cells, including stem cells, acquire and maintain their normal function, whereas cancer is a result of a cell breaking loose from its correct controls and becoming abnormal. Both areas require a detailed knowledge of intra- and intercellular processes, which need to be analysed at the cellular and molecular levels. These research areas are complementary at the scientific and technical levels. To understand what goes wrong when a cell becomes cancerous requires knowledge of the processes that ensure correct function in normal development. At the technical level, the analysis of cellular and molecular processes requires familiarity with techniques that no single person can master, such as gene cloning, antibody preparation, cell culture, microarray technology, imaging and embryonic manipulation. There is, therefore, a major benefit in having scientists with different but complementary knowledge and technical skills working in close proximity to one another.

The Institute is an integrated part of Cambridge University, and all Group Leaders are members of a University Department and contribute to teaching and graduate student supervision.

CENTRAL SUPPORT SERVICES

The Institute's 'core staff' provides administrative, technical and computing support to scientists, in order to ensure the smooth running of the Institute. During 2005 this has involved an enormous amount of work getting our new building up and running, and in particular coping with all the inevitable snags and breakdowns, while simultaneously carrying out their normal tasks. This juggling act has involved a great deal of hard work, and the Institute is grateful to every member of the core team.



FUNDING

Our two major funding bodies, the Wellcome Trust and Cancer Research UK, continue to offer the Institute vital backing in the form of Fellowships, individual project grants, and programme and equipment grants. As mentioned above, the Trust and CR-UK renewed the Institute's core funding from 2005.

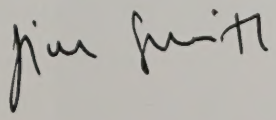
Other sources of financial support, both direct and indirect, include the European Community, BBSRC, the MRC, EPSRC, the Royal Society, the Lister Institute, the Isaac Newton Trust, the Leverhulme Trust, Beit Memorial Fellowships, the Association for International Cancer Research, NIH, the European Molecular Biology Organisation, and the March of Dimes. We are extremely grateful to all these organisations for their continuing support.

The University has also been very generous in its support of the Institute, particularly in funding equipment for the new building.

Annual retreat 2005, Lady Margaret Hall, Oxford (John Overton)

RETREAT

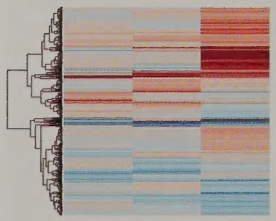
Our Annual Retreat was held yet again at Lady Margaret Hall, Oxford on 29th and 30th September 2005; this provides an ideal venue, allowing members of the Institute every opportunity to interact both scientifically and socially. As always there was a strong attendance and we are grateful to the administrative team and to Jon Pines and Magdalena Zernicka-Goetz for organising it.



Julie Ahringer

Patterning, cell polarity and genome-wide screening in *C elegans*

Co-workers: Rob Andrews, Yan Dong, Bruno Fievet, Nathalie Le Bot, Neeraj Mandhana, Costanza Panbianco, Gino Poulin, David Rivers, Frances Stedham, Miao-Chih Tsai, Christine Turner, David Welchman, Shane Woods



We study how patterns of cell divisions and cell fates are controlled, using *C elegans* as a model system. We have focused on two major questions: first, how is cell polarity established in the embryo and transduced within the cell? Second, how is chromatin regulated to effect cell fate decisions? For these studies, we are taking advantage of a genome-wide RNAi library that we have constructed.

Cell polarity is an essential feature of most animal cells. For example, it is critical for epithelial formation and function and for correct partitioning of fate-determining molecules. We use the large, transparent one-celled *C elegans* embryo as a simple yet powerful model system for studying cell polarity. Using genome-wide RNAi screening coupled with videomicroscopy of live embryos, we identified many new conserved cell polarity genes, which we study using genetics, biochemistry, and real-time fluorescent cell imaging.

Transcription repression is often mediated through histone deacetylase (HDAC) complexes. However, little is known about the developmental roles and regulation of histone deacetylation. In *C elegans*, HDAC complexes are involved in a range of different cell fate decisions, including inhibition of Ras signalling during vulval development. Through genome-wide RNAi screening, we have identified many new chromatin factors that cooperate with histone deacetylation. We are studying the function of these proteins in transcriptional control and their relationships to each other using chromatin immunoprecipitation and other techniques.

Inset left: Expression profiling of synMuv mutants using microarrays shows widespread gene expression changes compared to wild-type (dark red and dark blue colour in last row).

Ahringer J ed (2006) Reverse genetics, *WormBook*, ed The *C elegans* Research Community. **WormBook** doi/10.1895/wormbook.1.47.1 http://www.wormbook.org

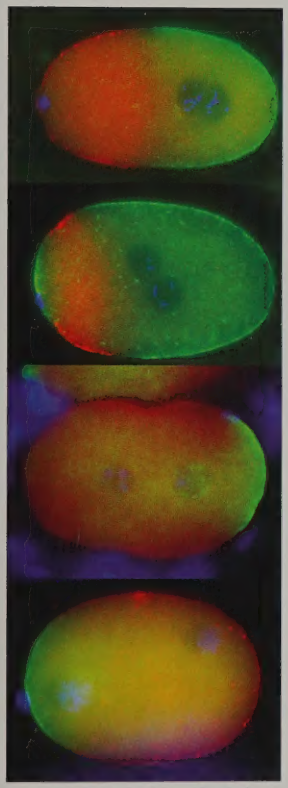
Poulin G, Dong Y, Fraser AG, Hopper N and Ahringer J (2005) Chromatin regulation and sumoylation in the inhibition of Ras-induced vulval development in *C elegans*. **EMBO Journal** 24, 2613–2623

Ahringer J (2005) Playing ping pong with pins: cortical and microtubule-induced polarity. **Cell** 123, 10-12.

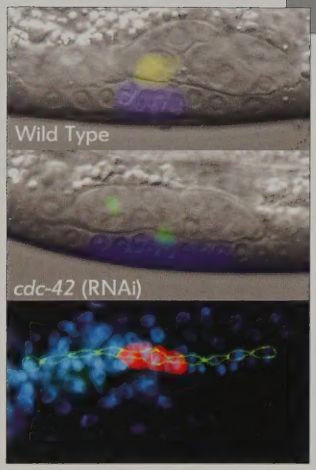
Gotta M, Dong Y, Peterson YK, Lanier SM and Ahringer J (2003) Asymmetrically distributed *C elegans* homologues of AGS3/PINS control spindle position in the early embryo. **Current Biology** 13, 1029-37

Kamath RS, Fraser AG, Dong Y, Poulin G, Durbin R, Gotta M, Kanapin A, Le Bot N, Moreno S, Sohrmann M, Welchman D, Zipperlen P and Ahringer J (2003) Systematic functional analysis of the *C elegans* genome using RNAi. **Nature** 421, 231-237

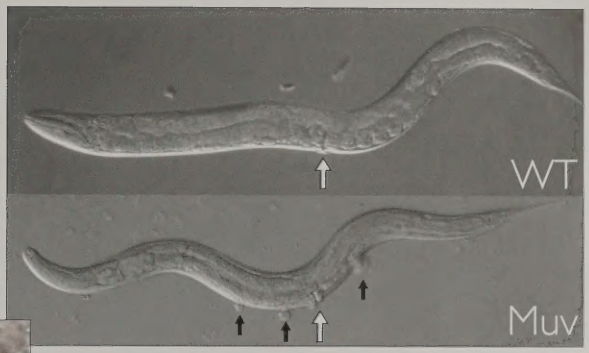
For complete list of this lab's publications since the last report, see numbers 2, 3, 64 & 65 on pp 55-62



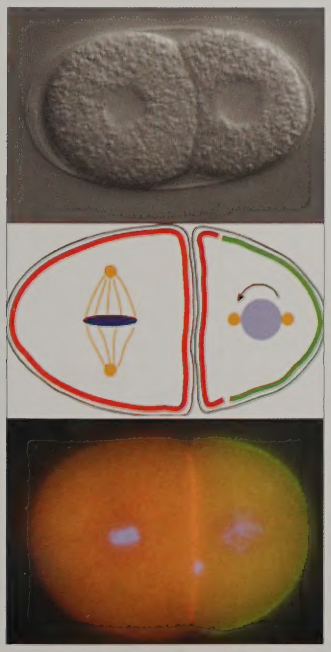
Abnormal distributions of polarity proteins PAR-3 (red) and PAR-2 (green) after RNAi of genes involved in establishing embryonic polarity. Top, wild-type, mutants below.



Fluorescent reporters for vulval and gonadal cells can be used to assay cell fates in live animals. Top two panels: primary vulval cells are blue, gonadal anchor cells are green/yellow; bottom panel: indirect immunofluorescence of a fixed animal outlines vulval cell junctions (green), primary vulval cells (red) and nuclei (blue).



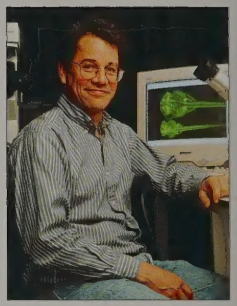
Ras signalling promotes vulval development and is antagonised by synMuv proteins, which are components of different chromatin regulatory complexes including the NuRD histone deacetylase and the TRRAP/TIP60 histone acetyltransferase complexes. Lack of synMuv function results in ectopic vulval tissue (black arrows, bottom), the multivulval (Muv) phenotypes. Wild type, top.



C elegans embryos are highly polarised. At the 2-cell stage, the anterior cell is larger than the posterior one, the two cells have different cortical proteins (PAR-3, red; PAR-2 green), different spindle orientations, and different cell cycle times.

Enrique Amaya

Growth factor signal interpretation in *Xenopus*



Co-workers: Juliet Barrows, Jun-an Chen, Ricardo Costa, Karel Dorey, Rosalind Friday, Kathy Hartley, Xiao Huang, Shoko Ishibashi, Nicholas Love

One of the main interests of our group is understanding the molecular events responsible for mesoderm formation and patterning. In particular we are investigating the role of fibroblast growth factor (FGF) signalling during mesoderm formation in the frog, *Xenopus*. We have shown that inhibiting FGF signalling during gastrulation disrupts mesoderm specification and morphogenesis. In order to better understand these processes, we have begun to isolate downstream targets of FGF signalling. We have identified Xsprouty2 as an important target gene. This protein and the related proteins, Xsprouty1, Xspred1 and Xspred2 are both targets and modulators of FGF signalling. We have recently shown that the Sprouty and Spred proteins play an important role in FGF signal interpretation, allowing mesoderm specification and morphogenesis to occur in a coordinated fashion.

In order to identify additional genes involved in mesoderm specification and morphogenesis, we are using bioinformatics tools in combination with functional screens to identify additional genes involved in these processes. As part of this project we have identified around 7000 full-length clones from *Xenopus tropicalis* and have screened nearly 2000 of these clones for genes affecting mesoderm formation and/or morphogenesis. Of those tested, we have isolated 82 genes, which alter or inhibit mesoderm formation and/or gastrulation movements.

In addition we are investigating the role of a novel D-type cyclin during the specification and maintenance of the motor neuron and interneuron precursors within the spinal chord of *Xenopus*. We are also studying the development of primitive myeloid cells, which give rise to the embryonic macrophages. Furthermore we are investigating their migratory behaviour, especially their recruitment to embryonic wound sites. Finally, we have begun to investigate the genes involved in the development and regeneration of the vasculature in *Xenopus*.

Inset left: Cranial nerves revealed in a transgenic stage-47 tadpole expressing placental alkaline phosphatase (PLAP) from the neural specific beta-tubulin promoter.

Amaya E (2005) Xenomics. **Genome Research** 15:1683–1691.

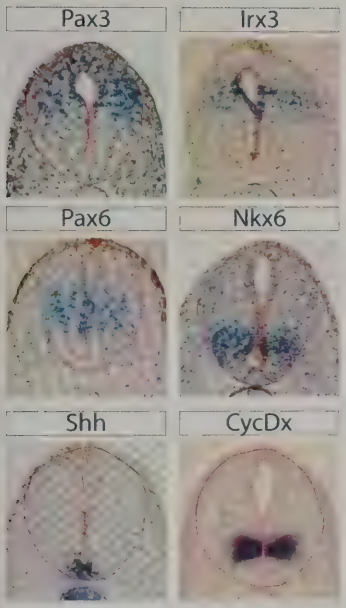
Sivak JM, Petersen L and Amaya E (2005) FGF Signal interpretation is directed by Sprouty and Spred proteins during mesoderm formation. **Developmental Cell** 8, 689-701

Chen J-A, Voigt J, Gilchrist M, Papalopulu N and Amaya E (2005) Identification of novel genes affecting mesoderm formation and morphogenesis through an enhanced large-scale functional screen in *Xenopus*. **Mechanisms of Development** 122, 307-331

Gilchrist M, Zorn AM, Smith JC, Voigt J, Papalopulu N and Amaya E (2004) Defining a large set of full length clones from a *Xenopus tropicalis* EST project. **Dev Biol** 271, 498-516

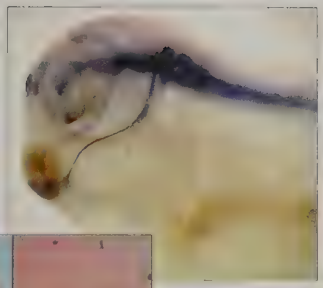
Voigt J, Chen J-A, Gilchrist M, Amaya E and Papalopulu N (2005) Expression cloning screening of a unique and full-length set of cDNA clones is an efficient method for identifying genes involved in *Xenopus* neurogenesis. **Mechanisms of Development** 122, 289-306

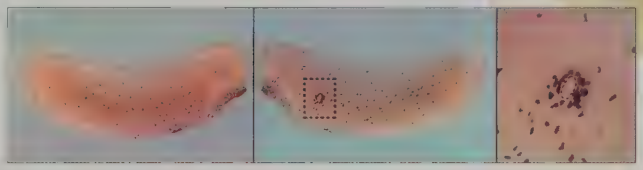
For complete list of this lab's publications since the last report, see numbers 6, 36 & 73 on pp 55-62



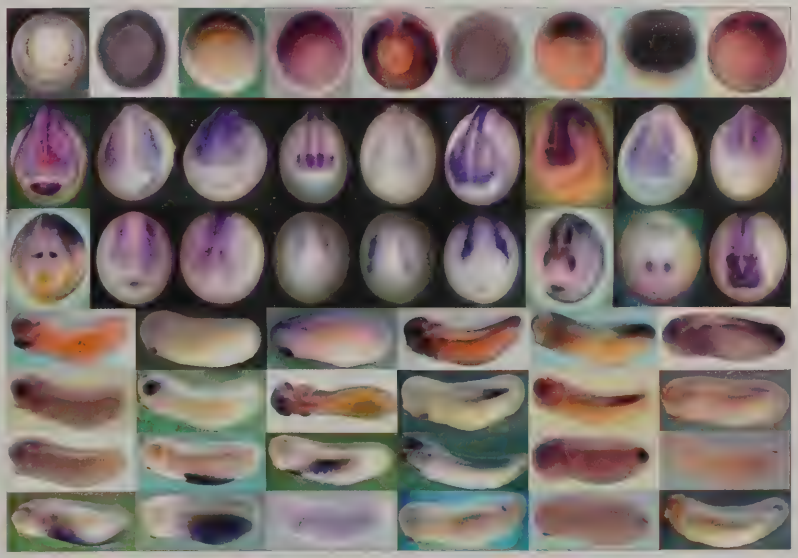
Cross sections of the spinal cord of *Xenopus* tadpoles stained for the expression of different markers along the dorso-ventral axis.

Trigeminal nerve in a transgenic stage-28 tadpole expressing placental alkaline phosphatase (PLAP) from the neural specific beta-tubulin promoter.





Primitive myeloid cells (dark spots) are present throughout the tailbud stage embryo. These three images are of the same embryo; the one on the left shows the right side of the embryo, the middle image shows the left side of the embryo, and the image on the right is a magnification of the area outlined in the middle image, where the primitive myeloid cells have congregated around an embryonic wound

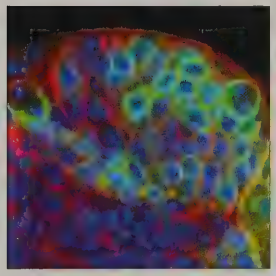


A montage of embryos showing the expression pattern of a select group of genes isolated in a large-scale gain of function screen aimed at identifying genes able to alter the specification and/or morphogenesis of the mesoderm. The top row shows embryos at the gastrula stages, the next two rows show embryos at the neurula stages and the bottom four rows show embryos at the tailbud stages

Andrea Brand

Embryonic nervous system development: stem cells to synapses

Co-workers: Torsten Bossing, Adrian Carr, James Chell, Semil Choksi, Melanie Cranston, Catherine Davidson, James Dods, Karin Edoff, Boris Egger, David Elliott, Ugo Mayor, John Solly, Tony Southall, Christine Turner



In the *Drosophila* nervous system, neural precursors (neuroblasts) divide in a stem cell-like fashion, renewing themselves at each division and giving rise to smaller daughter cells (GMCs) that divide only once before differentiating. Cell fate determinants, such as the transcription factor Prospero, are partitioned from neuroblasts to GMCs where they act to distinguish GMCs from their mothers. We are comparing the transcriptional networks of neuroblasts and GMCs to highlight the genes that regulate regenerative versus differentiative cell division. By identifying neural stem-cell-specific genes and genes specific for differentiating daughters we can begin to assess the potential for redirecting GMC-like cells to divide in a regenerative manner.

In vertebrates, adult neural stem cells can proliferate in response to injury. We have discovered that *Drosophila* ventral midline cells, which normally divide only once, can undergo an extra cell division if a sibling midline cell is destroyed. Remarkably, the regenerated midline cell differentiates appropriately to replace the damaged cell. Given its similarity to the vertebrate floorplate, the ventral midline may serve as a model system to study cellular regeneration in the vertebrate CNS.

We are also investigating the regulation of synaptic plasticity by localised protein degradation at synapses. One mechanism to control protein abundance is the ubiquitin-proteasome degradation system. Ubiquitin-mediated protein degradation is a central regulator of the eukaryotic cell cycle. A critical mediator of cell-cycle transitions is the anaphase-promoting complex/cyclosome (APC/C), an E3 ubiquitin ligase. We have shown that the APC/C plays a novel role in post-mitotic cells: it regulates synaptic growth and synaptic transmission at neuromuscular synapses.

Further information is available on the Brand Lab website:
http://www.gurdon.cam.ac.uk/~brandlab

Neural stem cells in the optic lobe reveal symmetric and asymmetric self-renewing divisions (Discs large in red; Partner of Numb-GFP in green; DAPI in blue).

Barros CS, Phelps CB and Brand AH (2003) *Drosophila* non-muscle myosin II promotes the asymmetric segregation of cell fate determinants by cortical exclusion rather than active transport. **Developmental Cell** 5, 829-840

van Roessel PJ, Elliott DA, Robinson IM, Prokop A and Brand AH (2004) Independent regulation of synaptic size and activity by the anaphase-promoting complex. **Cell** 119, 707-718

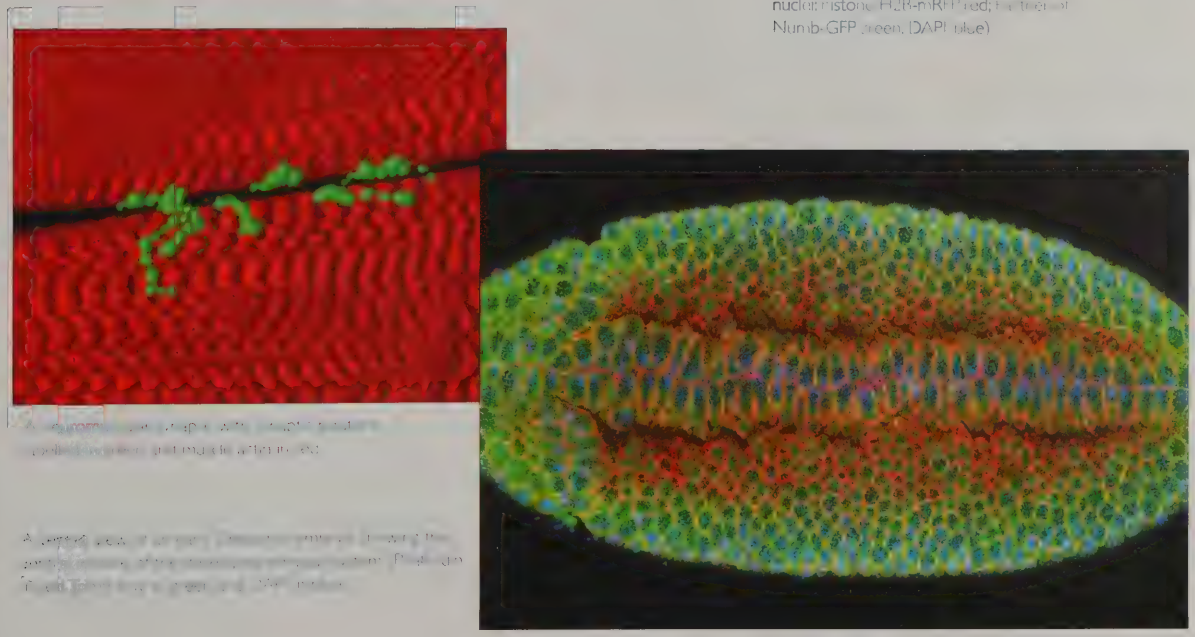
Dawes-Hoang RE, Parmar KM, Christiansen AE, Phelps CB, Brand AH and Wieschaus EF (2005) Folded gastrulation, cell shape change, and the control of myosin localization. **Development** 132, 4165-4178

Brand AH and Livesey FJ eds. (2005) Cell Differentiation. **Current Opinions in Cell Biology** vol 17 (6), 637-638

Bossing T and Brand AH (2006) Determination of cell fate along the antero-posterior axis of the *Drosophila* ventral midline. **Development**, [in press]

For complete list of this lab's publications since the last report, see numbers 14, 22, 25 & 83 on pp 55-62

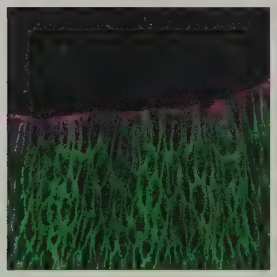
The developing visual system at a stage of a single confocal section of the eye imaginal disc (top), showing photoreceptor axons targeting the lamina neuropil and the optic lobe neuroblast (right), which divide asymmetrically to produce the ganglion cells of the medulla cortex (membranes: Discs large-red; nuclei: Histone H2B-mRFP red; the tip of Numb-GFP green; DAPI blue)



Nick Brown

Molecular analysis of morphogenesis

Co-workers: Isabelle Delon, Sven Huelsmann, Vanessa Maybeck, Maithreyi Narasimha, John Overton, Mary Pines, Katja Roeper, Dora Sabino, Esther Solomon, Xiao Tan, Guy Tanentzapf



Cellular adhesion and communication are vital during the development of multicellular organisms. These processes use proteins on the surface of cells, which stick cells together or transmit signals from outside the cell to the interior, so that the cell can respond to its environment. Members of one family of cell surface receptors, called integrins, can perform both of these activities, and therefore provide a molecular link between cell adhesion and signalling. Our research is focused on determining how proteins inside and outside the cell assist the integrins in their developmental roles: mediating cell migration, adhesion between cell layers and cell differentiation.

We use the genetics of the fruit fly *Drosophila* to elucidate integrin function within the developing animal and to identify the proteins that work with integrins. The majority of our work focuses on the intracellular proteins required for integrin function, many identified by a genetic screen we performed. As part of their function in mediating cell adhesion, integrins are linked to the cytoskeleton, in some cases prominant bundles of actin (Fig. 1). Several of the proteins required for integrin function, such as talin and tensin, contribute to this link (Fig. 2). Surprisingly, the cytoskeletal linker talin is also part of a signal transduction pathway that regulates the expression of the gene encoding another cell adhesion molecule, E-cadherin. A novel protein we have identified is very specifically localised in the dynamic leading edge cells (Inset left). We examined how the sequence differences of the 6 actin isoforms affect their ability to form different kinds of actin structures by tagging each actin with green fluorescent protein (GFP), and found that some actins become incorporated into particular structures much better than others (Fig 3). These new GFP-actins are being used to examine how integrins regulate the actin cytoskeleton within the living organism.

Inset left: A novel integrin-associated protein (purple) is expressed in the leading edge cells of the embryonic dorsal epidermis.

Bécam IE, Tanentzapf G, Lepesant J-A, Brown NH and Huynh J-R (2005) Integrin-independent repression of cadherin transcription by talin during axis formation in *Drosophila*. **Nature Cell Biol** 7, 510-516

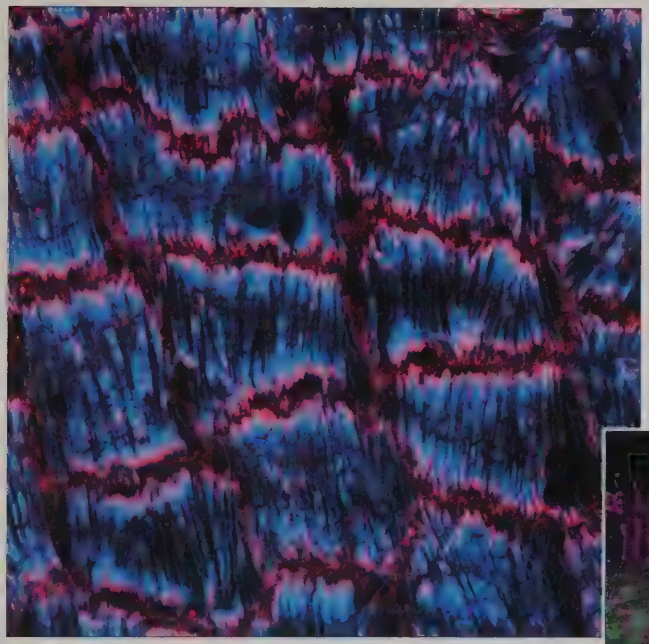
Röper K, Mao Y. and Brown NH (2005) Contribution of sequence variation in *Drosophila* actins to their incorporation into actin-based structures *in vivo*. **J Cell Sci** 118, 3937-3948

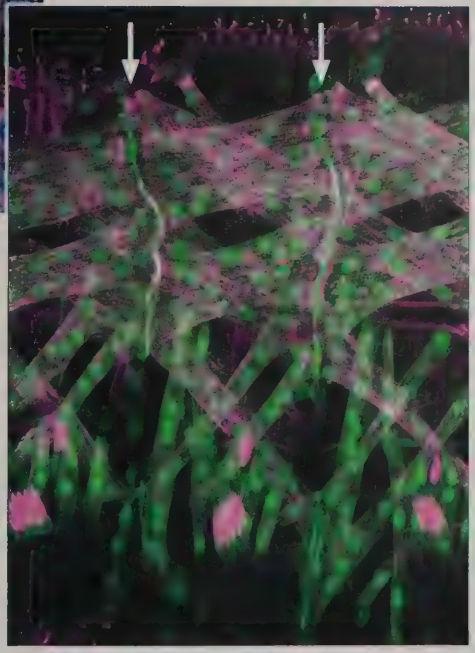
Narasimha M and Brown NH (2005) Integrins and associated proteins in *Drosophila* development. In **Integrins and development** Danen E, editor Landes Bioscience

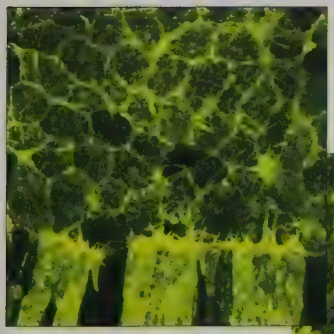
Bökel C, Prokop A, and Brown NH (2005) Papillote and Piopio, *Drosophila* ZP-domain proteins required for cell adhesion to the apical extracellular matrix and microtubule organization. **J Cell Sci** 118, 633-642.

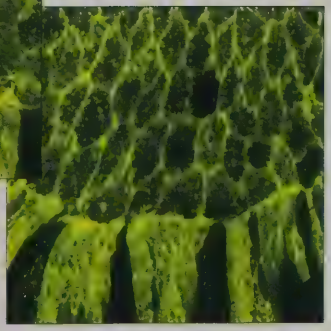
Bökel C and Brown NH (2002) Integrins in development: moving on, responding to, and sticking to the extracellular matrix. **Dev Cell** 3, 311-321

For complete list of this lab's publications since the last report, see numbers 12, 54, 55 & 67 on pp 55-62









John Gurdon

Reprogramming of gene expression by nuclear transfer

Co-workers: Adrian Biddle, Nigel Garrett, Jerome Jullien, Magda Koziol, Yen-Hsi Kuo, Kazutaka Murata, Ray Kit Ng, Ilenia Simeoni, Henrietta Standley, Caroline Webb

When the nuclei of differentiated cells are transplanted to enucleated eggs, multipotential embryonic cells can be obtained. These can be made to differentiate into a range of cell types unrelated to the original cells from which the nuclei were taken. This is the basis of a cell replacement strategy by which rejuvenated cells can be derived from an adult cell. These newly-generated cells are of the same genetic constitution as the donor cell, and are therefore suitable for cell replacement therapy without the need for immunosuppression. We aim to identify the molecules and to understand the mechanisms by which the reprogramming of gene expression takes place. The same experiments give valuable information about the mechanisms that stabilise cell differentiation during normal development, and that therefore need to be reversed for cell rejuvenation.

Our principal method of analysis involves transplanting multiple nuclei from adult tissues such as the mouse thymus into the growing oocytes of *Xenopus*. Within 2 days, or within a few hours for the nuclei of less specialised cells, the transplanted nuclei express genes such as Oct4 and Nanog, which are diagnostic of embryo or stem cells. We analyse the reprogramming of gene expression at several levels. We have found that oocytes have a DNA demethylating activity that reverses differentiation by acting on the promoter of Oct4. We use extracts of oocytes to identify, and test the function of, oocyte components that bind to the promoter region of Oct4. We use confocal microscopy to view in real time the binding of defined proteins to somatic cell nuclei as they undergo gene reprogramming.

In related work, we are analysing the epigenetic memory of an active gene state in certain examples of somatic cell nuclear transfer. We are also analysing the mechanisms by which cells can memorise an extracellular concentration of morphogen long after the morphogen has been removed.

Inset left: The germinal vesicle of a *Xenopus* oocyte. The bright spots represent nucleoli and cajal bodies

Ng RK, and Gurdon JB (2005). Epigenetic memory of active gene transcription is inherited through somatic cell nuclear transfer. **Proc Natl Acad Sci USA** 102, 1957-1962

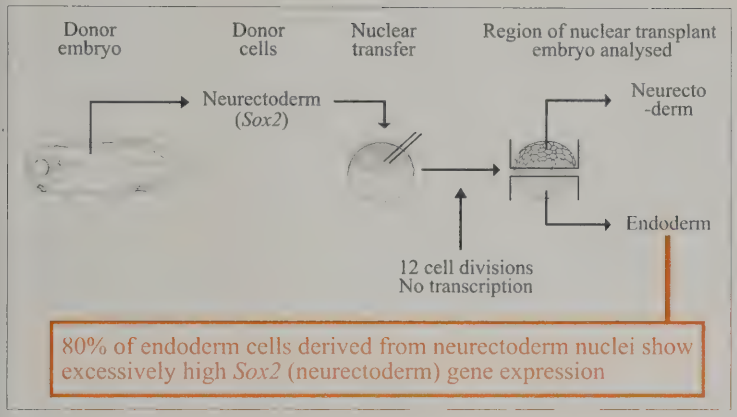
Jullien J, and Gurdon JB (2005). Morphogen gradient interpretation by a regulated trafficking step during ligand-receptor transduction. **Genes Dev** 19, 2682-2694

Simonsson S, and Gurdon JB (2004). DNA demethylation is necessary for the epigenetic reprogramming of somatic cell nuclei. **Nature Cell Biology** 6, 984-990

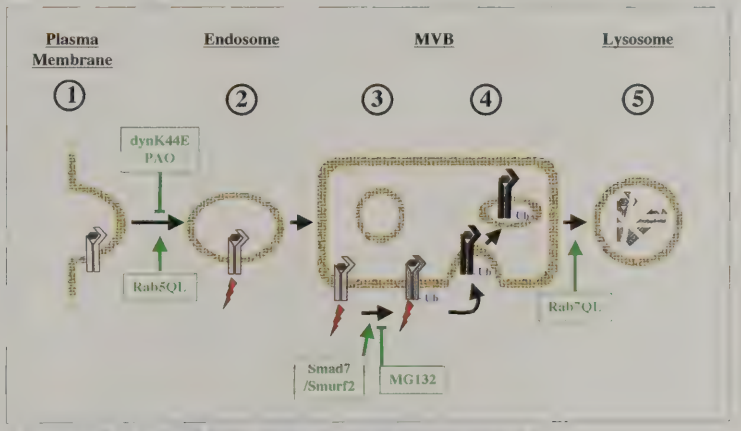
Gurdon JB, Byrne JA, and Simonsson S (2003). Nuclear reprogramming and stem cell creation. **Proc Natl Acad Sci USA** 100, 11819-11822

Byrne JA, Simonsson S, Western PS, and Gurdon JB (2003). Nuclei of adult mammalian somatic cells are directly reprogrammed to oct-4 stem cell gene expression by amphibian oocytes. **Curr Biol** 13, 1206-1213

For complete list of this lab's publications since the last report, see numbers 29, 30, 31, 32, 33, 34 40, 56, 57 & 71 on pp 55-62



Transplanted nuclei have epigenetis memory



prolonged dwell time of the ligand-receptor complex at step 3

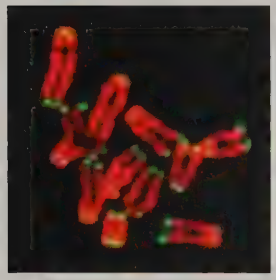
Xenopus oocyte extract
+
Oct4 promoter oligos
↓
Gel shift
↓
Isolate DNA-protein complex
↓
Purify Xenopus protein
↓
Identify equivalent mouse protein
↓
Knock down protein from mouse ES cell
↓
See Oct4 depletion in ES cells

Identification of Oct4 promoter binding proteins

Steve Jackson

Maintenance of genome stability in eukaryotic cells

Co-workers: Peter Ahnesorg, Rimma Belotserkovskaya, Richard Chahwan, Julia Coates, Robert Driscoll, Kate Dry, Yaron Galanty, Sabrina Giavara, Serge Gravel, Jeanine Harrigan, Pablo Huertas, Alicia Lee, Christine Magill, Andreas Meier, Abdel Moumen, Venkat Pisupati, Helen Reed, Alex Sartori, Philippa Smith



The DNA damage response (DDR) has evolved to optimise cell survival following DNA damage. It involves the actions of DNA repair proteins together with the "checkpoint" events that slow down or arrest cell-cycle progression while the damage is being removed. Our aim is to determine – at the molecular level – how cells detect DNA damage then trigger the DDR. As these events have been highly conserved throughout eukaryotic evolution, we are using the combined approach of studying them both in yeast and in mammalian cells.

Over the past year, we have made exciting progress in several areas. For example, we have established that the three principle mammalian DDR kinases – DNA-PKcs, ATM and ATR – are recruited to sites of DNA damage by homologous mechanisms involving their direct interactions with related, conserved C-terminal motifs in the proteins Ku80, NBS1 and ATRIP, respectively (Figure 1)[1]. Furthermore, we have discovered that phosphorylation of the histone variant H2AX by the above kinases creates a phospho-peptide docking site for the DDR mediator protein MDC1, and moreover that this interaction is required for the focal assembly of MCD1 and other DDR factors on damaged chromatin and efficient DNA double-strand break repair (Figure 2)[2,3]. In addition, by a proteomics approach we have established that heterogeneous nuclear ribonucleoprotein K (hnRNP K) is rapidly induced in response to DNA damage[4]. In addition to defining the mechanism for this induction, we have found that hnRNP K promotes DNA damage induced cell cycle arrests by serving as a transcriptional cofactor for p53 (Figure 3). Finally, with our colleagues we have established that inhibitors of the DDR protein PARP1 are selectively cytotoxic to cells lacking the tumour suppressor proteins BRCA1 or BRCA2. This raises the exciting prospect that PARP inhibitors will have utility in treating hereditary breast and ovarian cancers[5].

1) Falck J, Coates J, Jackson SP (2005) Conserved modes of recruitment of ATM, ATR and DNA-PKcs to sites of DNA damage. **Nature** 434(7033), 605-611

2) Goldberg M, Stucki M, Falck J, D'Amours D, Rahman D, Pappin D, Bartek J and Jackson SP (2003) MDC1 is required for the intra-S-phase DNA damage checkpoint. **Nature** 421(6926), 952-956

3) Stucki M, Clapperton J, Mohammad D, Yaffe MB, Smerdon SJ and Jackson SP (2005) MDC1 directly binds phosphorylated histone H2AX to regulate cellular responses to DNA double-strand breaks. **Cell** 123, 1213-1226

4) Moumen A, Masterson P, O'Connor M and Jackson SP (2005) HnRNP K: an HDM2 target and transcriptional co-activator of p53 in response to DNA damage. **Cell** 123, 1065-1078

5) Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, Martin NM, Jackson SP, Smith GC, Ashworth A (2005) Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. **Nature** 434(7035), 917-21

For complete list of this lab's publications since the last report, see numbers 23, 27, 28, 37, 39, 42, 43, 53, 66, 70, 79 & 89 on pp 55-62

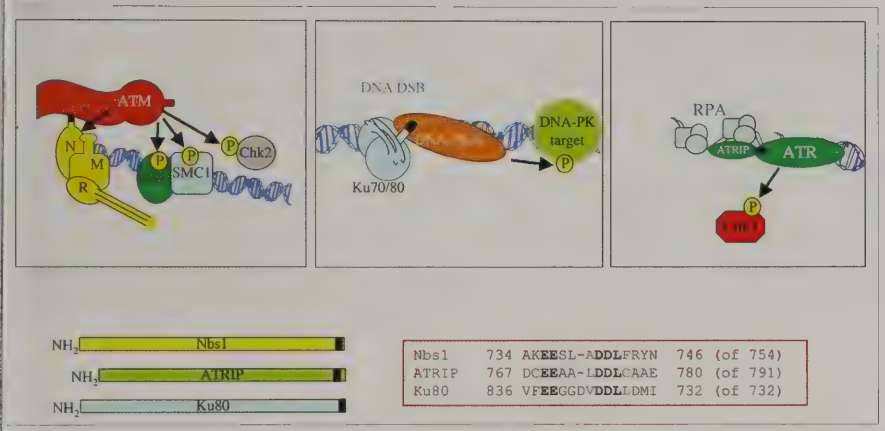


Fig 1: Unified DNA-damage recruitment and activation mechanism for DDR-kinases. Recruitment of these kinases to sites of DNA damage allows efficient phosphorylation of key downstream target proteins.

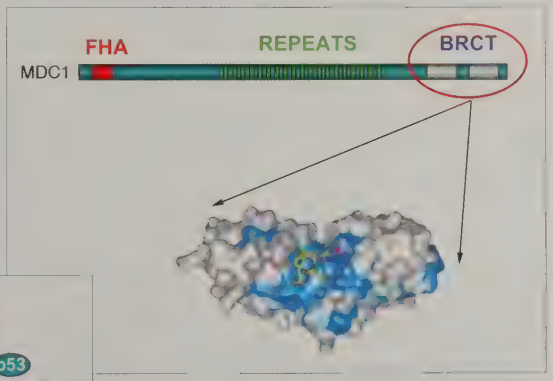


Fig 2: Structure of the MDC1 BRCT-γH2AX tail complex. γH2AX phosphopeptide binds in an extended conformation to a groove shaped by the interface between the 2 BRCT repeats. Residues with 100% conservation are shaded dark blue while highly conserved residues are shaded light blue. The structural data were generated by our collaborators S Smerdon and J Clapperton (NIMR, London).

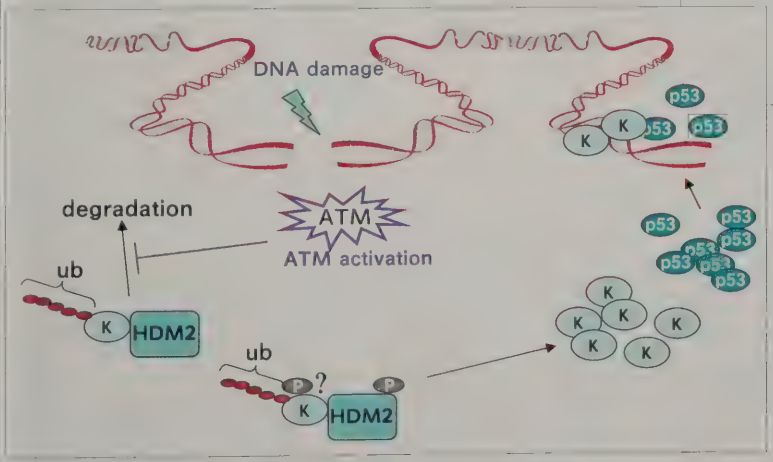
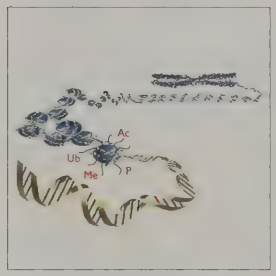


Fig 3: hnRNP K acts as a cofactor in p53 transcriptional responses. Following DNA damage, hnRNP K is rapidly induced in an ATM-dependent manner through the inhibition of Hdm2/Mdm2 mediated proteosomal degradation. Subsequently, hnRNP K and p53 co-assemble on the promoters of p53 target genes leading to their transcriptional activation. (Done in collaboration with M. O'Connor (KuDOS Pharmaceuticals)

Tony Kouzarides

Function of Chromatin Modifications

Co-workers: Andrew Bannister, Till Bartke, Gill Collins, Alistair Cook, Sophie Deltour, Karen Halls, Paul Hurd, Rachel Imoberdorf, Antonis Kirmizis, David Lando, Susana Lopes, Chris Nelson, Claire Pike, Helena Santos Rosa



Our group is interested in defining the mechanisms by which chromatin modifications function to regulate cellular processes. Our attention is focused on a set of enzymes (acetylases, deacetylases, methylases and kinases), which regulate transcription by covalently modifying histones. We would like to understand what biological processes these enzymes control and the precise role of each modification on chromatin dynamics. In addition, a number of chromatin modifying enzymes have been implicated in the genesis of cancer so we are dissecting as far as possible, in the pathways misregulated in cancer cells.

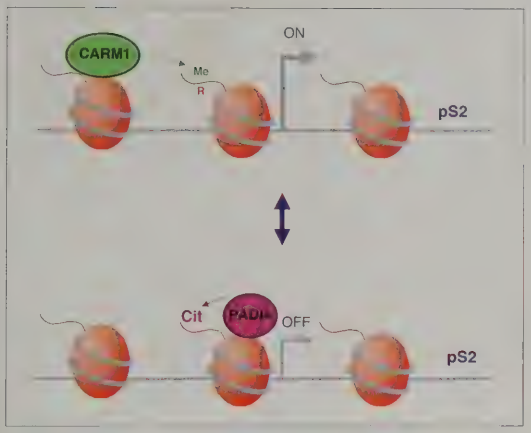
We are taking a number of complimentary approaches to characterise chromatin modifications. We use yeast as a model system whenever possible, since it has a much simpler modification pattern. Our recent analysis of methylation at histone H4K20 has shown that this modification has a role in DNA repair. We are now using Chromatin Immunoprecipiation experiments on a genome-wide yeast array to map the position of all known and some novel modifications. We are also reconstituting recombinantly, nucleosomes carrying specific combinations of modifications, in order to understand how they affect transcription, how they affect compaction of chromatin and to identify specific proteins that recognise them.

Histones are very highly modified, but we believe that more modifications are likely to exist on histones. This complexity is probably necessary because histones integrate many signalling pathways with biological processes involving DNA metabolism and function. A major drive at the moment is to identify new histone-modifying enzymes, as the pathways they control may well be deregulated in cancer. Recently we have characterised a novel modification, deimination, which is the conversion of arginine to citrulline. The deiminating enzyme PADI4 is present in vertebrates and has a role in antagonising the methylation of arginine residues in the tail of histone H3. Deimination results in the down-regulation of genes involved in estrogen signalling.

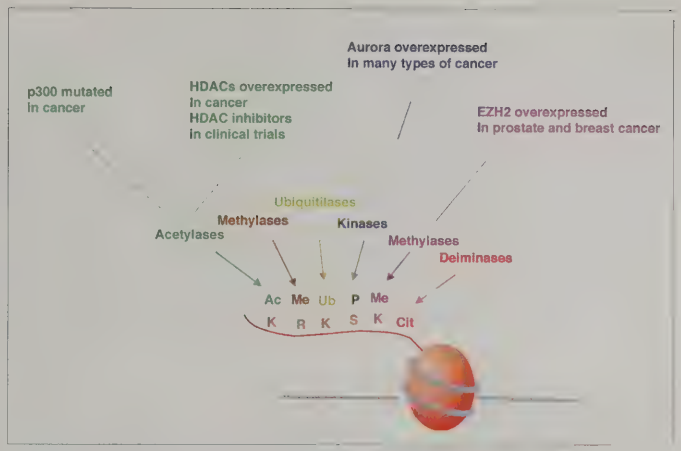
Cuthbert GL, Daujat S, Snowden AW, Erdjument-Bromage H, Hagiwara T, Yamada M, Schneider R, Gregory PD, Tempest P, Bannister JA and Kouzarides T (2004) Histone deimination antagonises arginine methylation. **Cell** 118, 545-553

Sanders SL, Portoso M, Mata J, Bahler J, Allshire RC and Kouzarides T (2004) A role for histone H4 and lysine 20 methylation in DNA damage response. **Cell** 119, 603-614

For complete list of this lab's publications since the last report, see numbers 7, 8, 9, 17, 26, 72 & 77 on pp 55-62

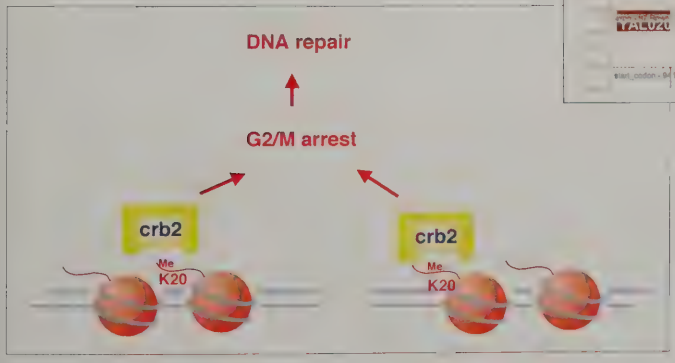


The PADI4 deiminase antagonises arginine methylation and represses transcription.



Chromatin modifying enzymes are deregulated in cancer.

Genomic pattern of methylation at all currently known methylation sites in yeast (part of chromosome 1 shown).

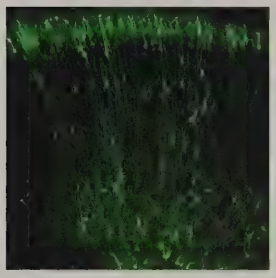


Methylation of H4K20 recruits the CrB2 protein to mediate G/2M arrests and allows cells to repair damaged DNA.

Rick Livesey

Neural cell fate determination: development and evolution of the cerebral cortex

Co-workers: Juliet Barrows, Dean Griffiths, Grace Nisbet, Sabhi Rahman, Stephen Sansom, James Smith, Tatiana Soubkhankoulova, Uruporn Thammongkol



Building a nervous system depends on two fundamental processes: the production of many different types of neurons vy multipotent neural stem and progenitor cells, and the wring of those neurons together to make functional circuits. We study the first of these processes, how the correct types of neurons are generated in the appropriate places and times from stem and progenitor cells, using the neocortex as a model system.

The neocortex, the part of the brain that integrates sensations, executes decisions and is responsible for cognition and perception, is a region of the nervous system that is unique to mammals. It is also a highly evolved part of the brain, exhibiting striking differences in relative size and complexity between different mammalian species, including primates. Morphologically, the neocortex is a large, sheet-like structure, composed of six layers of neurons. However, the neocortex is a modular structure, with different areas of the six-layered sheet connected to different parts of the nervous system and thereby devoted to different functions. Thus, there are modules primarily dedicated to, for example, motor control, the somatic senses, vision and hearing.

Our two primary research questions are:

- how are neurons destined for each of the six layers generated in a temporal order by neocortical stem and progenitor cells?

- how are neocortical areas formed, or how are area-specific neurons produced by neocortical stem and progenitor cells?

We refer to the first question as the timing problem and the second as the patterning problem. We use a number of different approaches in mice and chicks to address these problems, with a particular emphasis on genomics and systems biology methods. We also have an active interest in the clinical application of our findings, particularly in the aetiology and pathogenesis of autistic spectrum conditions.

Inset left: Differentiating neocortical neurons (green, GFP expressing): live confocal image of a cortical slice four days after electroporation of a GFP-expressing plasmid into neocortical progenitor cells

Sansom SN, Hebert JM, Thammongkol U, Smith J, Nisbet G, Surani MA, McConnell SK and Livesey FJ (2005) Genomic characterisation of a Fgf-regulated gradient-based neocortical protomap. **Development** 132, 3947-61

Livesey FJ, Young TL and Cepko CL (2004) An analysis of the gene expression program of mammalian neural progenitor cells. **Proc Natl Acad Sci USA** 101, 1374-9

Blackshaw S and Livesey R (2002) Applying genomics technologies to neural development. **Curr Opin Neurobiol** 12, 110-4

Livesey FJ, Furukawa T, Steffen MA, Church GM and Cepko CL (2000) Microarray analysis of the transcriptional network controlled by the photoreceptor homeobox gene Crx. **Curr Biol** 10, 301-10

For complete list of this lab's publications since the last report, see numbers 14 & 69 on pp 55-62

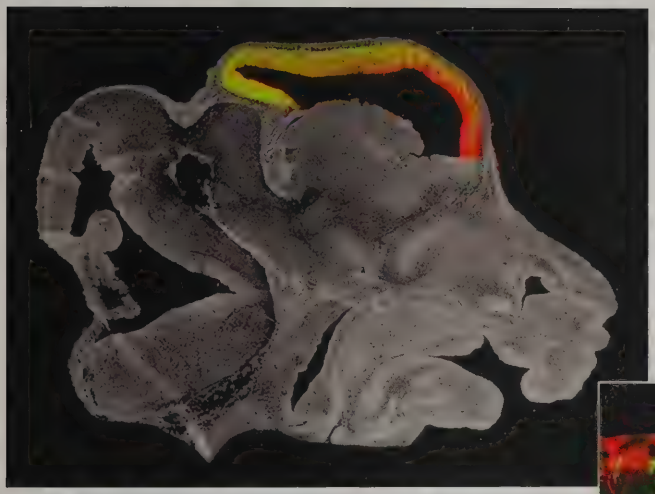


Fig 1. A readout of neocortical patterning is front-to-back (red) and back-to-front (green) gradients of expression of transcription factors across the developing neocortex as shown by two-colour fluorescent *in situ* hybridisation.

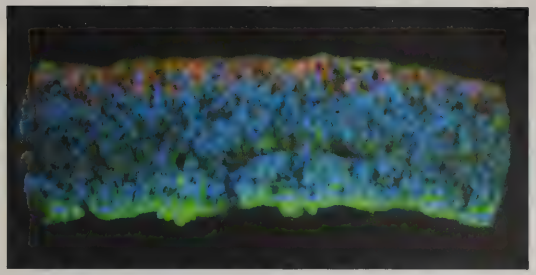


Fig 2. Stem and progenitor cells (green – nestin expressing) in the neocortical ventricular zone generate neurons (red – beta-tubulin expressing) that migrate vertically to populate the cortical plate.

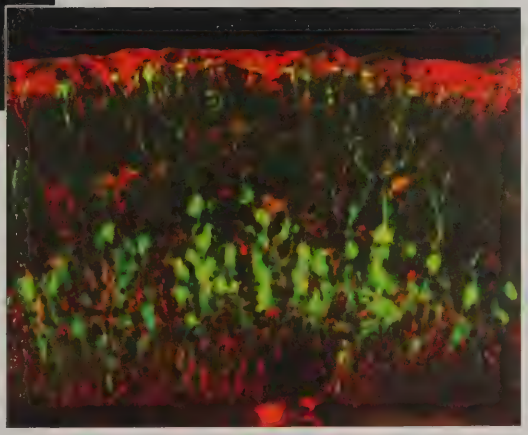
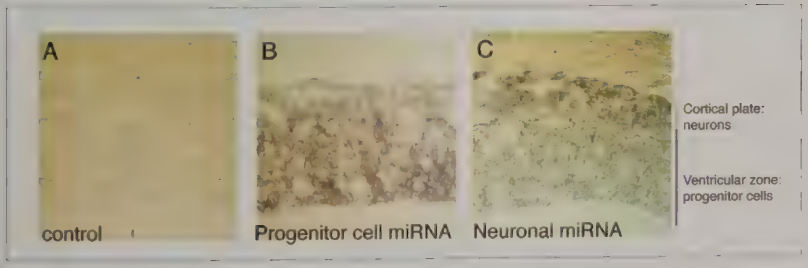


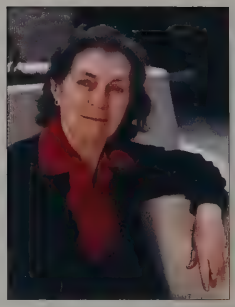
Fig 4. Gain and loss of function studies of transcription factors in neocortical explant culture system by electroporation of expression constructs that also express GFP.

Fig 3. Microarray analysis of microRNA expression in the developing neocortex identified microRNAs with specific expression in either neocortical stem and progenitor cells (B) or in differentiating neurons (C).

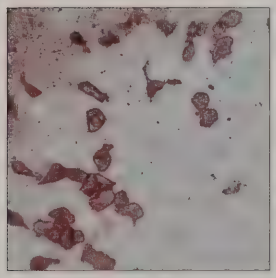


Anne McLaren

The development of mouse primordial cells



Co-workers: Dilly Bradford, Susana Chuva de Sousa Lopes, Tanya Shovlin



Our research focuses on mouse primordial germ cells (PGCs), on the pluripotent stem cells derived from them (EG cells), and on the epigenetic changes that both PGCs and EG cells undergo.

Although PGCs themselves express FGF2, the derivation of EG cells from PGCs requires the addition of exogenous FGF2 to the culture medium in a dose-dependent manner, for the first few hours of culture. In the presence of an adequate level of FGF2, the FGF2 receptor FGFR-3 is translocated from the cytoplasm into the nucleus in a small proportion of the PGCs. We believe that it is this subset of PGCs that undergoes nuclear reprogramming and phenotypic changes, giving rise to pluripotent EG cells.

The sex-specific methylation of differentially methylated sites in imprinted genes is erased in PGCs during and after their migration from the base of the allantois where the germ cell lineage is established, to the site of the future gonads. We already know that EG cells derived from PGCs during and shortly after migration show significantly less site-specific methylation than their progenitor PGCs, suggesting that the erasure process may continue in the PGCs after they have been placed in culture. We are now looking at the methylation status of EG cells made from earlier PGC stages, before migration has begun.

Inset left: PGC-containing region of a E7.5 mouse embryo cultured for 24 hours and stained for alkaline phosphatase activity

Facing page: Expression of FGFR-3 protein in both freshly-isolated and cultured PGCs by immunofluorescence. PGCs were identified with antibodies to Oct-4 or SSEA-1 (green) or FGFR-3 (red). DNA is stained in blue. (a-c) Freshly-isolated 8.5 dpc PGCs express FGFR-3 at low levels. (d-f) Cultured PGCs exposed only to LIF express FGFR-3 in PGC cytoplasm. Under those conditions EG cells are never derived. (g-i) 8.5 dpc PGCs cultured for 24 hours in LIF and FGF-2 (conditions required for deriving EG cells). High expression of FGFR-3 is detected in nuclei and cytoplasm of a few PGCs. (j-l) After 4-5 days small colonies are observed. All cells in colonies express FGFR-3 in cytoplasm and nuclei. (m-o) Cell suspension of EG cells and feeder cells. EG cells express FGFR-3 in both nuclei and cytoplasm

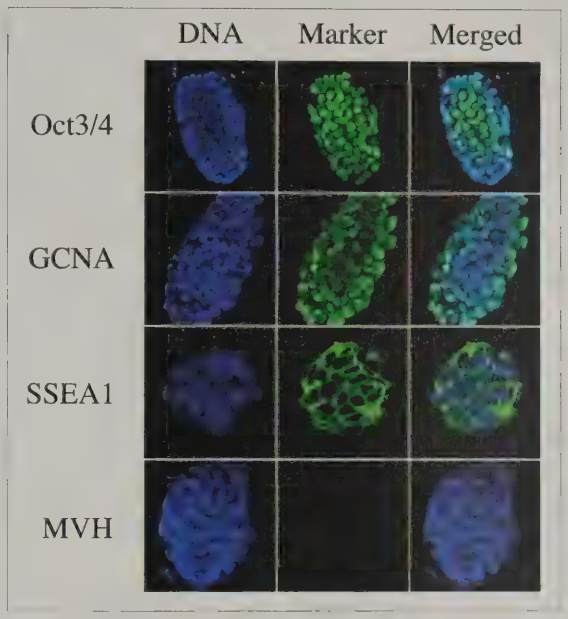
Telfer EE, Gosden RG, Byskov AG, Spears N, Albertini D, Andersen CY, Anderson R, Braw-Tal R, Clarke H, Gougeon A, McLaughlin E, McLaren A, McNatty K, Schatten G, Silber S and Tsafriri A (2005) On regenerating the ovary and generating controversy. **Cell** 122, 821-822

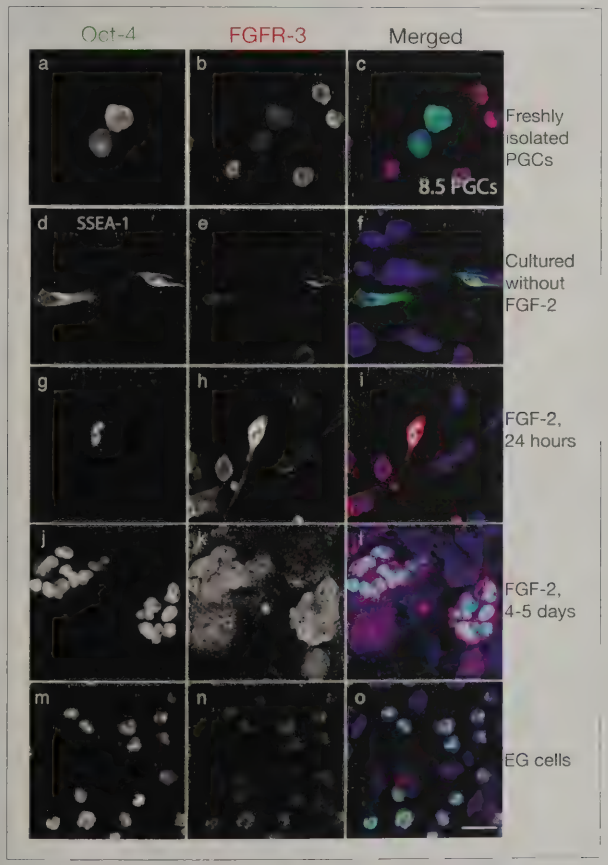
McLaren A and Lawson KA (2005) How is the mouse germ-cell lineage established? **Differentiation** 73, 435-437

McLaren A (2005) Chapters 13 and 39 (with G Durcova-Hills) in **Essentials of Stem Cell Biology**, R Lanza (Ed) Elsevier-Academic Press.

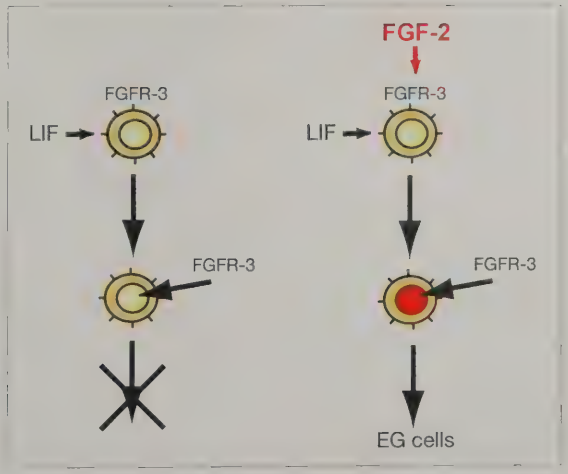
For complete list of this lab's publications since the last report, see numbers 24, 45, 46, 47, 48, 49 & 82 on pp 55-62

Right: Markers of undifferentiated pluripotent EG cells. Oct-4 (nuclear), GCNA (nuclear), and SSEA1 (cell surface) are present. PGC marker MVH is not detected in EG cells. DNA is stained in blue.





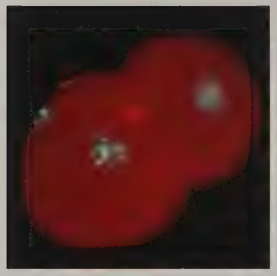
Right: PGCs cultured in LIF alone do not form EG cells. FGFR-3 is detected only in the cytoplasm of PGCs after 24 hours of culturing. However, when FGF-2 is added to the culture, FGFR-3 is translocated into the nucleus of cultured PGCs. These suggest that these PGCs are close to EG cells.



Masanori Mishima

Molecular mechanism of cytokinesis

Co-workers: Recruitment to Dr Mishima's research group will begin in 2006.



Cytokinesis is essential for cell proliferation. Failure of cytokinesis leads to aneuploidy or chromosomal instability, which has been associated with human cancers. Successful cytokinesis relies on a dynamic interplay between microtubules, the actin cytoskeleton, and membrane compartments under the control of the cell cycle machinery. In spite of its importance, the molecular mechanism of cytokinesis in animal cells has not yet been fully clarified.

We would like to understand cytokinesis more fully, in terms of dynamic assembly of molecular machinery. The central spindle is a microtubule-based molecular assembly that forms between the segregating chromosomes during anaphase. During telophase, it associates with the ingressing cleavage furrow and matures into the midbody. These microtubule-based structures have crucial roles through all the steps of cytokinesis from initiation to completion. We will address the following questions:

- How is the central spindle/midbody assembled?
- How does the central spindle/midbody contribute to the progression of cytokinesis at the molecular level?

We will focus on centralspindlin, a stable protein complex of a mitotic kinesin-like protein and a Rho-family GTPase-activating protein (RhoGAP), which is crucial for assembly of the central spindle and the midbody. We will characterise the dynamic behaviour of centralspindlin and investigate centralspindlin-interacting proteins by using mammalian cultured cells and *Caenorhabditis elegans* embryos as model systems. In addition to biochemical and genetical analyses, live imaging both at single molecule level *in vitro* and at subcellular level *in vivo* will be performed. We will also develop experimental strategies to (in)activate molecules of interest *in vivo* in a reasonable time resolution to dissect the molecular mechanism of cytokinesis

A *C elegans* embryo finishing cytokinesis. Centralspindlin (red) is highly concentrated to the midbody when chromosomes are reforming nuclei (cyan).

Guse A, Mishima M and Glotzer MA (2005) Conserved role for Aurora B phosphorylation of ZEN-4/MKLP1 in completion of cytokinesis. **Curr Biol** 15, 778-86

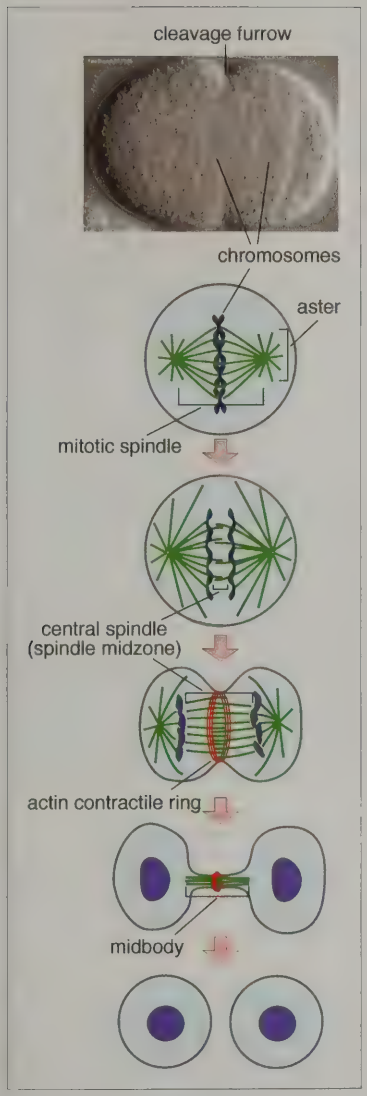
Mishima M, Pavicic V, Grüneberg U, Nigg EA, and Glotzer M (2004) Cell cycle regulation of central spindle assembly. **Nature** 430, 908-13

Mishima M, and Glotzer M (2004) Cytokinesis. In **Encyclopedia of Biological Chemistry** (WJ Lennarz & MD Lane eds), Elsevier, Oxford, vol 1, pp. 556-62

Mishima M and Glotzer M (2003) Cytokinesis: a logical GAP. **Curr Biol** 13, R589-91

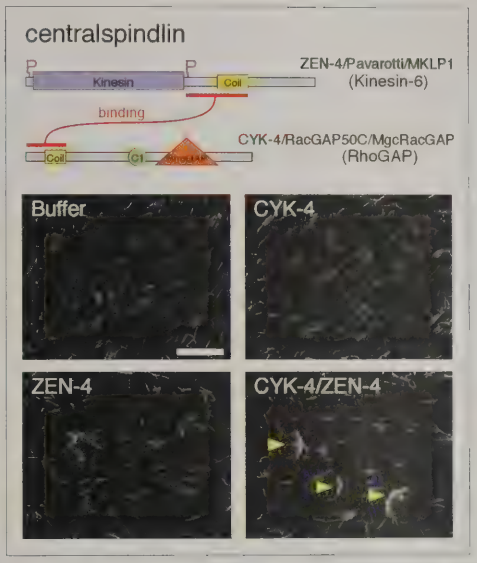
Mishima M, Kaitna S and Glotzer M (2002) Central spindle assembly and cytokinesis require a kinesin-like protein/RhoGAP complex with microtubule bundling activity. **Dev Cell** 2, 41-54

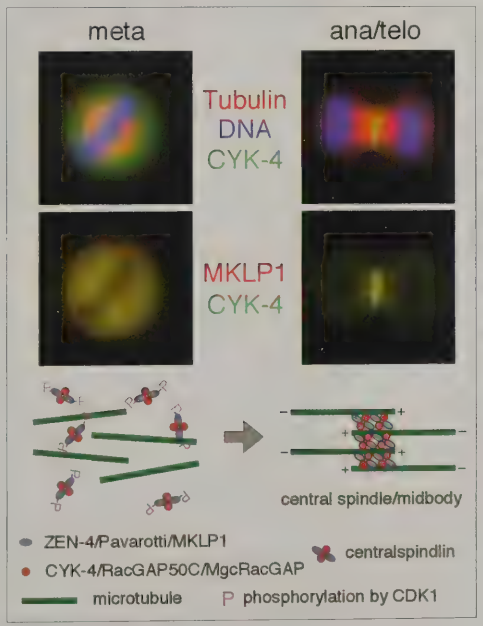
For complete list of this lab's publications since the last report, see numbers 35 & 38 on pp 55-62



Cytokinesis

Centralspindlin is an evolutionarily conserved protein complex of [illegible] microtubule-bundling activity. When incubated with microtubules, the complex causes the strong bundling of microtubules (arrowheads), while neither the kinesin subunit alone nor the RhoGAP subunit alone does





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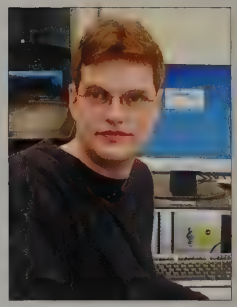
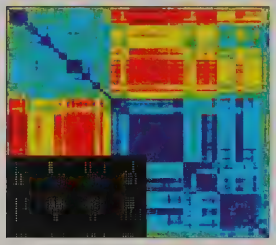
Eric Miska

Control of gene expression through non-coding DNA



Co-workers: Cherie Blenkiron, Heeran Buhecha, Partha Pratim Das, Robert Shaw, Abhimanyu Veerakumarasivam



The recent discovery of microRNAs has added a completely new dimension to the control of eukaryotic gene expression. MicroRNAs are a large class of 18-26 nucleotide short regulatory RNAs. Approximately 1% of all known human genes encode microRNAs, but very little is known about their biological roles. Our laboratory is interested in understanding how microRNAs contribute to the determination of cell fate, ie the decision to divide, die or differentiate, and how deregulation of microRNAs may contribute to disease, in particular to cancer.

We use the powerful genetics of the nematode *Caenorhabditis elegans* to study the function of microRNAs. Our starting point is a collection of microRNA knockout strains covering the majority of all known microRNA genes in this organism. To place microRNAs into biological pathways we combine phenotypic analysis, expression studies, genetic screens and bioinformatics.

We are also interested in the mechanism of microRNA action. Currently we are focusing on the Argonaute family of RNA-binding proteins, which have been implicated in both the mechanism of RNAi and microRNA pathways. Of particular interest to us are the orthologues of two *Drosophila Argonaute* family members, Aubergine and Piwi that define germ line identity in the fly. We use a combination of biochemical and genetic approaches to understand their function.

In invertebrates microRNAs have been implicated as regulators of developmental timing (e.g. *lin-4*), neuronal differentiation, cell proliferation, programmed cell death and fat metabolism. In contrast, no in vivo function for any microRNA has been established in mammals. To help uncover the biological roles of microRNAs in mammals we first ask the question where and when microRNAs are expressed using microarray profiling. One focus is the analysis of microRNA expression in primary human tumours. This work is being carried out as a collaboration with the Cancer Genomics Group at the Broad Institute of MIT, and Harvard.

Inset left: We have developed microRNA microarrays to profile microRNA expression in *C elegans* and mammals (insert). We compare the expression of microRNAs in different tissues, at different stages during development and under a variety of physiological conditions to understand where microRNAs act and how their expression is regulated. Shown here is a correlation heat map.

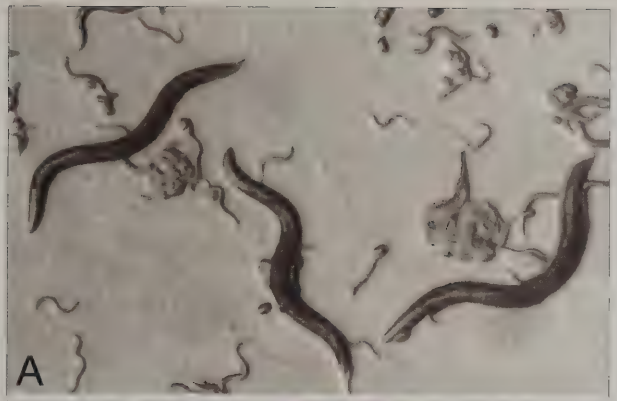
Alvarez-Garcia I, Miska EA (2005) MicroRNA functions in animal development and human disease. **Development** 132, 4653-4662

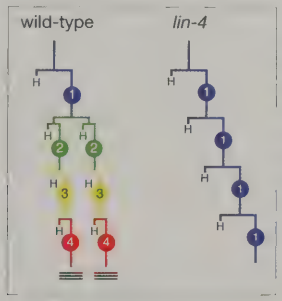
Abbott AL*, Alvarez-Saavedra E*, Miska EA*, Lau NC, Bartel DP, Horvitz HR, Ambros V (2005) The let-7 MicroRNA family members mir-48, mir-84, and mir-241 function together to regulate developmental timing in *Caenorhabditis elegans*. **Dev Cell** 9, 403-414 (* equal contribution)

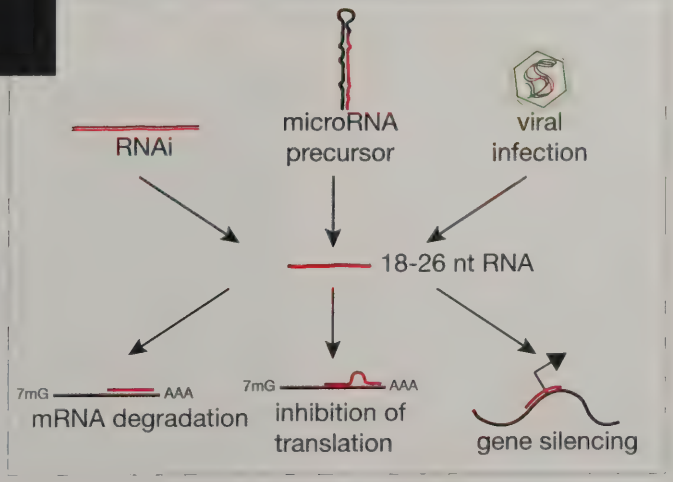
Miska EA (2005) How microRNAs control cell division, differentiation and death. **Curr Opin Genet Dev** 15, 563-568

Miska EA, Alvarez-Saavedra A, Townsend M, Yoshii A, Sestan N, Rakic P, Constantine-Paton M, Horvitz HR (2004) Microarray analysis of microRNA expression in the developing mammalian brain. **Genome Biology** 5(2), R60

For complete list of this lab's publications since the last report, see numbers 1, 4, 5, 44, 51 & 87 on pp 55-62





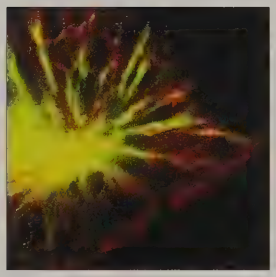


Short RNAs as key players of gene regulation: Primary microRNA gene transcripts contain stem-loop structures that are processed to RNAs by type III enzymes such as Dicer to give rise to the mature miRNA. Dicer is also required for the processing of double-stranded viral RNA and for generating siRNAs in RNAi. microRNAs can participate in the initiation of translational inhibition, RNA degradation, and possibly transcriptional gene silencing.

Nancy Papalopulu

Molecular control of neurogenesis in vertebrate embryos

Co-workers: Eva Asscher, Juliet Barrows, Julia Mason, Tarik Regad, Martin Roth, Bernhard Strauss



During embryonic development neuroectodermal cells exit the cell cycle and differentiate in a stereotypical spatial and temporal pattern. Other cells remain undifferentiated and serve as stem cells for growth and later waves of neurogenesis. We aim to understand how the balance of differentiation and progenitor maintenance is achieved and we use the frogs *Xenopus laevis* and *Xenopus tropicalis* as model systems.

We are studying the function and regulation of localised transcription factors, such as FoxG1, a master gene controlling neurogenesis and cell division in the forebrain. Our current emphasis is on the role of protein modifications that serve to integrate signalling pathways in controlling the activity of FoxG1. In parallel, we are using *Xenopus* microarrays to identify target genes in order to decipher the gene networks controlling differentiation in the forebrain.

Neuronal differentiation is also controlled by the intrinsic competence of the cells to differentiate. This is the result of asymmetric cell divisions of polarised cells that generate outer polar and inner apolar cells on the neural plate. We have found that only inner apolar cells are competent to participate in early neurogenesis while outer polar cells have a propensity to remain as undifferentiated progenitor cells to the end of embryogenesis. In these cells, aPKC is located on the apical membrane and Lgl-2 on the basolateral side. By gain and loss of function experiments we have shown that an antagonistic interaction between aPKC and Lgl-2 defines the proportion of specialised apical and basolateral membrane in these cells. We are now investigating whether these membrane asymmetries influence the transcriptional program of the neuroepithelial cells. By microarray analysis, we have identified several genes that are specific for polarised or apolar cells of the neural plate and their function is now investigated.

Finally, gain and loss of function screens based on a *X tropicalis* EST project, has uncovered novel genes that affect many aspects of neural development.

Inset left: Dynein-decorated (red) astral microtubules (green) of *Xenopus* blastula cells. (Bernhard Strauss)

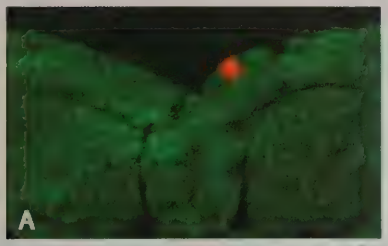
Voigt J and Papalopulu N (2006) A dominant negative Cullin-1, an E3 ubiquitin ligase, disrupts the correct allocation of cell fate in the neural crest lineage. **Development** [in press]

Chalmers A, Pambos M, Lang S, Wylie C and Papalopulu N (2005) aPKC, crumbs3 and Lgl 2 control apical/basal polarity in early vertebrate development, **Development** 132, 977-986

Voigt J, Chen JA, Gilchrist M, Amaya E and Papalopulu N (2005) Expression cloning screening of a unique and full-length set of cDNA clones is an efficient method to identify gene function in *Xenopus* neurogenesis, **Mech Dev** 122, 289-306

Chalmers AD, Strauss B and Papalopulu N (2003) Oriented cell divisions asymmetrically segregate aPKC and generate cell fate diversity in the early *Xenopus* embryo. **Development** 130, 2657-68

For complete list of this lab's publications since the last report, see numbers 62 and 84 on pp 55-62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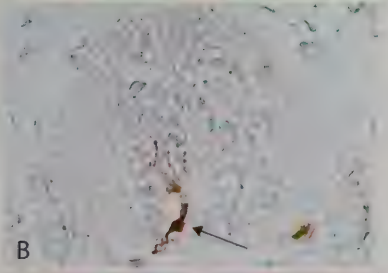
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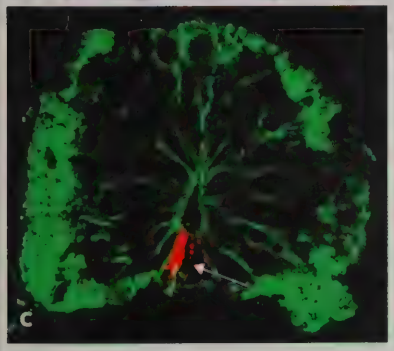
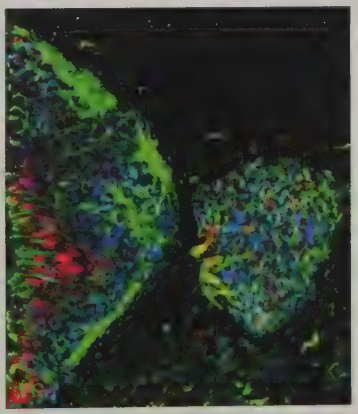

C


FoxG1
DAPI
merged


N-tubulin
XSox3
FoxG1

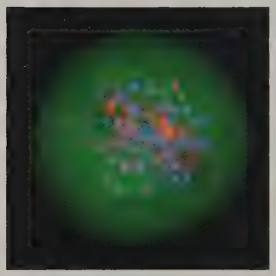


Jonathon Pines

How do cells control mitosis?

Co-workers: Claire Acquaviva, Caroline Broad, Lorena Clay, Fay Cooke, Barbara Di Fiore, Alex Domin, Suzanne Floyd*, Olivier Gavet, Anja Hagting, Mark Jackman, Lars Koop, Catherine Lindon*, Takahiro Matsusaka, Jakob Nilsson

* Suzanne is working with Catherine Lindon (independent MRC Fellow).



How do cells regulate entry to mitosis? And, once in mitosis, how do cells coordinate the remarkable events of chromosome alignment and segregation with cell division itself (cytokinesis) to ensure that the two daughter cells receive an equal and identical copy of the genome? The answer seems to lie in the interplay between mitotic kinases and phosphatases and ubiquitin-mediated proteolysis, in particular ubiquitination mediated by the Anaphase Promoting Complex/Cyclosome (APC/C). Because mitosis is a highly dynamic process we are studying these processes in living cells by time-lapse fluorescence microscopy. We use FRAP and photo-activation to gain a better understanding of the kinetics of protein behaviour, deconvolution to improve the spatial resolution and FRET to assay protein-protein interaction and kinase activity.

To understand how cells first initiate mitosis we are analysing the behaviour of the mitotic cyclin-CDKs, cyclins A and B1, and their regulation by phosphorylation and subcellular localisation. We use GFP-fusion proteins to reveal the dynamics of protein localisation through the cell cycle, and to define how proteins are targeted to specific subcellular structures. To identify the proteins responsible for targeting we are analysing protein complexes by mass spectrometry.

To understand how proteolysis is used to regulate progress through mitosis we assay the degradation of the GFP-fusion proteins in living cells. These studies are beginning to reveal how the APC/C is first activated and, most importantly, how it is able to select a particular protein for destruction at a specific time in mitosis to coordinate events such as chromosome segregation and cytokinesis. We have strong evidence that the ubiquitination machinery is spatially regulated in mitosis and we are investigating whether this is responsible for the exquisite control of protein degradation by the spindle assembly checkpoint. We hope that these studies will increase our understanding of how cells control their division to prevent improper chromosome segregation (aneuploidy) that is the hallmark of many cancer cells.

Inset left: prometaphase cell stained with Aurora B (red), centromeres (red) and Emi1 (green). (Barbara di Fiore)

Acquaviva C, Herzog F, Kraft C and Pines J (2004) The Anaphase Promoting Complex/Cyclosome is recruited to centromeres by the spindle assembly checkpoint. **Nature Cell Biology** 6, 892-898

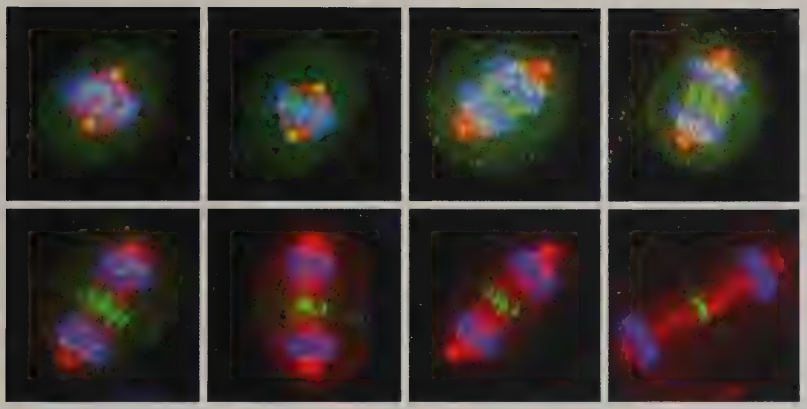
Matsusaka T and Pines J (2004) Chfr acts with the p38 stress kinase to block entry to mitosis in mammalian cells. **J Cell Biol** 166, 507-516

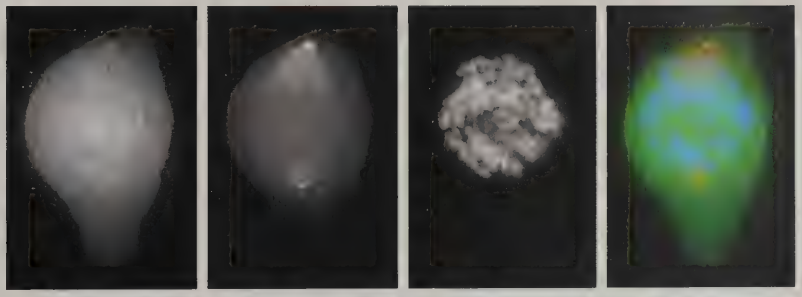
Lindon C and Pines J (2004) Ordered proteolysis in anaphase inactivates Plk1 to contribute to proper mitotic exit in human cells **J Cell Biol** 164, 233-241

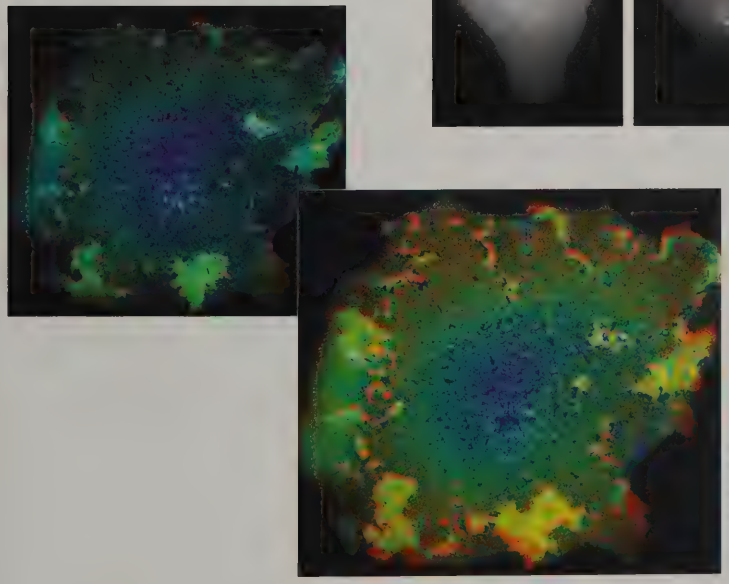
Jackman M, Lindon C, Nigg EA and Pines J (2003) Active cyclin B1-Cdk1 first appears on centrosomes at the end of prophase. **Nature Cell Biol** 5, 143-148

Hagting A, den Elzen N, Vodermaier HC, Waizenegger IC, Peters J-M and Pines J (2002) Human securin proteolysis is controlled by the spindle checkpoint and reveals when the APC/C switches from activation by Cdc20 to Cdh1. **J Cell Biol** 157, 1125-1137

For an additional publication since the last report, see number 59 on pp 55-62



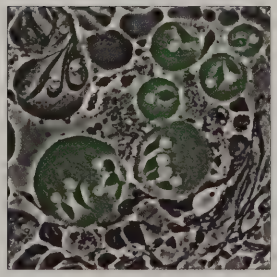




Jordan Raff

Molecular analysis of the centrosome

Co-workers: Teresa Barros, Renata Basto, Sue Croysdale, Carly Dix, Jeroen Dobbelaere, Joyce Lau, Eliana Lucas, Nina Peel, Naomi Stevens



The centrosome is the main microtubule organising centre in animal cells. Using *Drosophila* as a model system, we are studying several centrosomal proteins in order to understand how centrosomes function at the molecular level. D-TACC is essential for stabilising microtubules in embryos, and it appears to recruit the microtubule stabilising protein Minispindles (Msps) to centrosomes. We have shown that D-TACC is phosphorylated by Aurora A on a site that is conserved between fly, human, and frog TACC proteins, and this phosphorylation event occurs exclusively at centrosomes (Fig 1). A form of D-TACC that cannot be phosphorylated by Aurora A is only partly functional: mitotic spindles are largely normal, but astral MTs are destabilised (Fig 2). Thus, it appears that the phosphorylation of D-TACC by Aurora A allows D-TACC to stabilise only centrosomal MTs. We propose that Aurora A functions to ensure that centrosomes are the major site of MT nucleation during mitosis by activating D-TACC exclusively at centrosomes. Excitingly, in collaboration with the Hyman laboratory in Dresden, we have shown that a similar mechanism operates in *Xenopus* eggs.

What are the essential functions of centrosomes in a developing organism? We have been studying a centriolar protein called DSas-4 that is essential for centriole replication in flies (Fig 3). In DSas-4 mutants, centrioles are gradually lost during development as the maternal supply of protein is exhausted. Amazingly, we find that morphologically normal mutant flies are born with near normal timing at near normal rates, even though the vast majority of mutant cells appear to completely lack centrioles and centrosomes (Figs 4 and 5). A careful examination of these flies is underway, but early signs indicate that many cell processes are inefficient in the absence of centrosomes, but that flies can somehow compensate and development is not dramatically perturbed.

Inset left: Centrioles are essential for cilia and flagella formation. Phase contrast image showing the localisation of a centriolar marker GFP-PACT (green) during spermatid elongation.

Barros T, Kinoshita K, Hyman AA and Raff JW (2005) Aurora-A activates D-TACC/Msps complexes exclusively at centrosomes to stabilise centrosomal MTs. **J Cell Biol** 170, 1039-1046

Kinoshita K, Noetzel TL, Pelletier L, Mechtler K, Drechsel DN, Schwager A, Lee M, Raff JW, and Hyman AA (2005) Aurora A phosphorylation of TACC3/Maskin is required for centrosome dependent microtubule assembly in mitosis. **J Cell Biol** 170, 1047-1055.

Chodagam S, Royou A, Whitfield W, Karess R, and Raff JW (2005) The centrosomal protein CP190 regulates myosin function during early *Drosophila* development. **Curr Biol** 15, 1308-1313

Martinez-Campos M, Basto R, Baker J, Kernan M, and Raff JW (2004) The *Drosophila* pericentrin-like protein is essential for cilia/flagella function but appears to be dispensable for mitosis. **J Cell Biol** 165, 673-683

Raff JW (2004) Centrosomes in a developing organism: lessons from *Drosophila*. In: **Centrosomes in Development and Disease**. Nigg EA Ed, Wiley-VCH

For complete list of this lab's publications since the last report, see numbers 11, 18 & 41 on pp 55-62

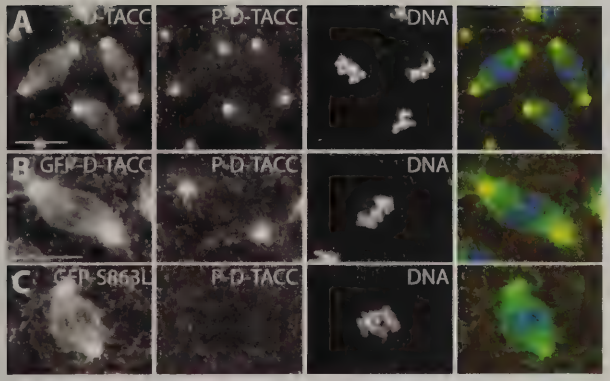


Fig 1: (A) The localisation of D-TACC (Green) and Phospho-D-TACC (Red) in Drosophila embryos (DNA is shown in Blue). (B,C) D-TACC null mutant embryos that express either GFP-D-TACC or GFPS863L (a form of D-TACC that cannot be phosphorylated by Aurora A) probed to reveal the distribution of D-TACC (green) and Phospho-D-TACC (Red). No Phospho-D-TACC is detectable in the GFPS863L embryo

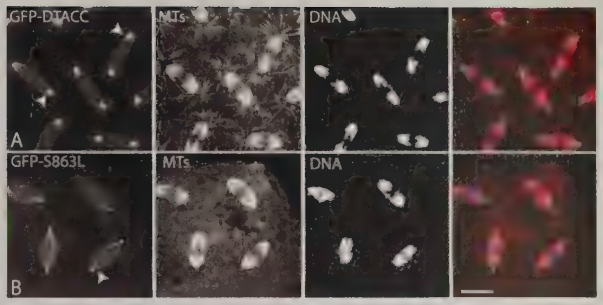


Fig 2: The localisation of MTs (Red), DNA (Blue) and either GFP-D-TACC or GFP-S863L (Green) in D-TACC null mutant embryos that express one of these proteins. (A) GFP-D-TACC is seen to localise to centrosomes and spindle MTs, apparent by the presence of MTs. (B) GFP-S863L also seems to centrosomes and spindle MTs, although less than GFP-D-TACC.

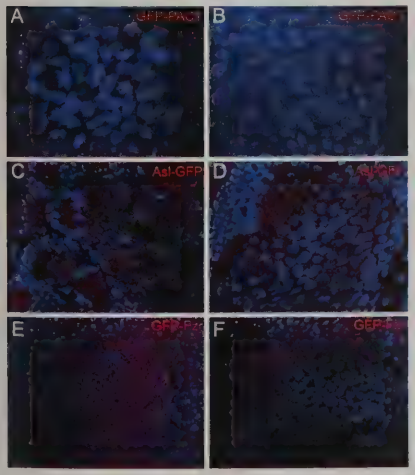
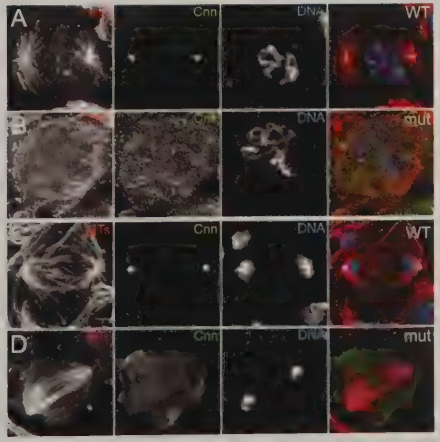
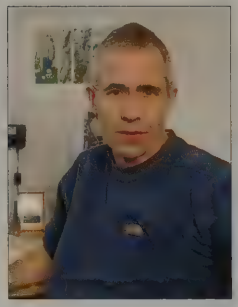


Fig 3: The localisation of GFP-PACT (Aat-GFP and GFP-PACT in centrosomes in WT brain neuroblasts. PACT and Aat have been shown to be detectable with at the centrosomes in DSpd-2 mutant brains. (E,F)

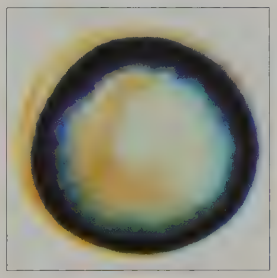


Jim Smith

Molecular basis of mesoderm formation



Co-workers: Joanna Argasinska, Julia Bate, Liz Callery, Clara Collart, Kevin Dingwell, Amanda Evans, Anja Hagemann, Kim Lachani, Nigel Messenger, Oliver Nentwich, Joana Ramis, Amer Rana, Yasushi Saka, Fiona Wardle, Xin Xu



Work in our laboratory is aimed at understanding the molecular basis of mesoderm formation. We hope to identify the signals that cause mesoderm to form, to understand how they can exert their effects at long range and in a concentration-dependent manner, to identify the genes that are activated by the mesoderm-inducing signals, and to determine how these genes contribute to the regulatory network that underlies mesodermal differentiation. We hope that our work will assist in efforts to direct embryonic stem cells down particular developmental pathways and, eventually, allow us to make differentiated cells move backwards in developmental time, so that they can then be re-programmed as the experimenter desires.

Our work makes use of *Xenopus* species (both *laevis* and *tropicalis*) and, more recently, the zebrafish. We are using genomic resources in both species to help us isolate new genes involved in mesoderm formation, and to identify their partners and transcriptional targets. We are also carrying out an antisense morpholino oligonucleotide screen to study the functions of large numbers of genes in *Xenopus* tropicalis, and we plan to ask to what extent the results obtained in this amphibian species will apply to mammalian embryos.

One particular interest concerns the mechanisms by which inducing factors exert long-range effects in the early embryo, and we are studying this by means of tagged forms of inducing factors such as Xnr2 and by using novel approaches to identify cells that are responding to such signals. In common with other members of the transforming growth factor type β family, Xnr2 exerts its effects by causing Smad proteins to form heteromeric complexes, and another aspect of our work has been to identify and characterise Smad-interacting proteins such as SmicI.

Additional experiments address morphogenetic processes in the early embryo, including gastrulation and neurulation, and we continue to study the regulation and function of members of the T box family of proteins, the founder member of which is Brachyury.

Inset left: Whole mount *in situ* hybridisation showing the expression of the *Xenopus* T box gene Xbra at the early gastrula stage.

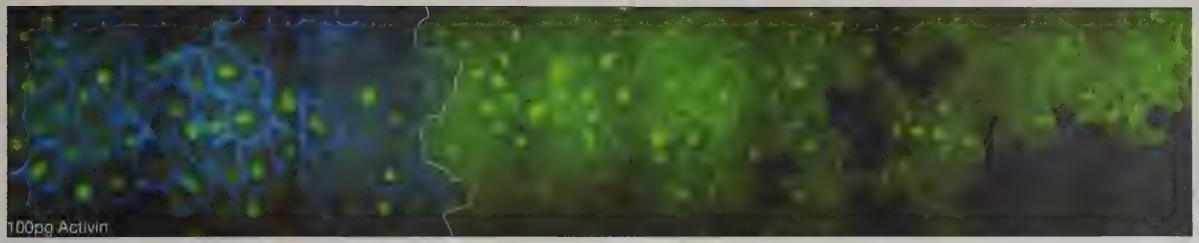
Messenger NJ, Kabitschke C, Andrews R Grimmer, D, Núñez Miguel R, Blundell TL, Smith JC and Wardle FC (2005) Functional specificity of the T-domain protein Brachyury is conferred by its ability to interact with Smad1. **Developmental Cell** 8, 599-610

Collart C, Verschueren K, Rana A, Smith JC and Huylebroeck D (2005) The novel Smad-interacting protein SmicI regulates Chordin expression in the *Xenopus* embryo. **Development** 132, 4575-4586

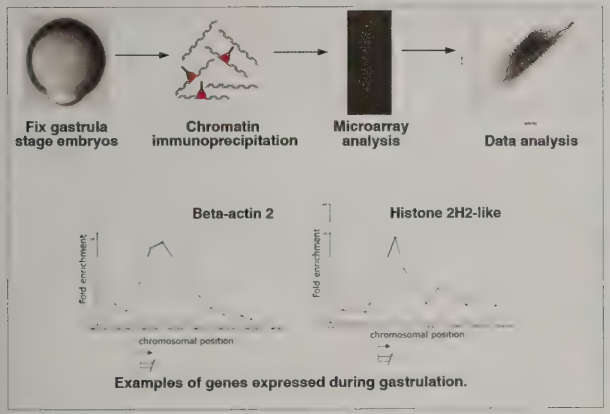
Taverner NV, Kofron M, Shin Y, Kabitschke C, Gilchrist MJ, Wylie C, Cho KWY, Heasman J and Smith JC (2005) Microarray-based identification of VegT targets in *Xenopus*. **Mech Dev** 122, 333-354

Callery EM, Smith JC and Thomsen GH (2005) The ARID domain protein dril1 is necessary for TGFβ signaling in *Xenopus* embryos. **Dev Biol** 278, 542-559

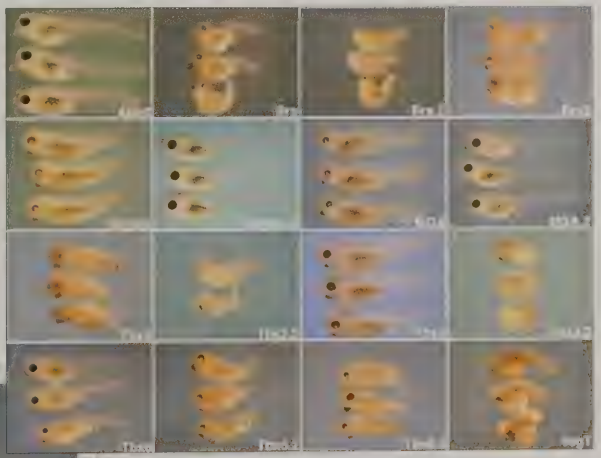
For complete list of this lab's publications since the last report, see numbers 13, 15, 16, 20, 50, 74, 75, 76, 81 & 85 on pp 55-62



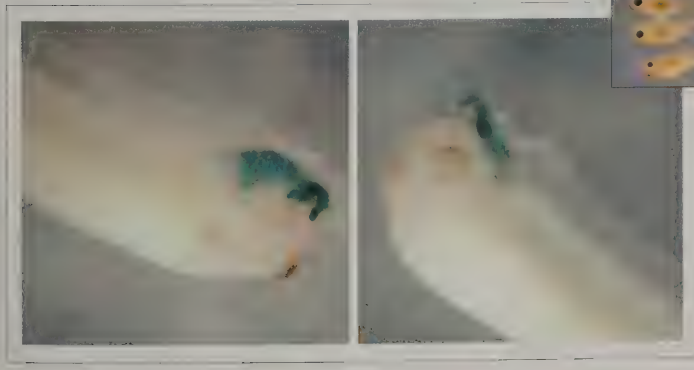
Activin expressed in cells whose membranes are stained blue (left) can activate Smad signaling (green nuclei, right) at a distance



Chromatin immunoprecipitation combined with genomic microarrays identifies actively transcribed genes in the zebrafish gastrula embryo



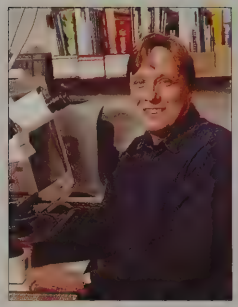
...of a large-scale antisense morpholino oligonucleotide screen, we have inhibited the functions of all known T box genes expressed during gastrula stage



...s in the head of a *Xenopus* embry...

Daniel St Johnston

mRNA localisation and the origin of polarity in *Drosophila*



Co-workers: Katsiaryna Belaya, Chin-Wen Chang, Sue Croysdale, Katja Dahlgaard, Eurico De Sa, Helene Doerflinger, Celia Faria, Alejandra Gardiol, Jacqueline Hall, Uwe Irion, Nick Lowe, Vincent Mirouse, Trent Munro, Alexandre Raposo, Isabel Torres, Vitaly Zimyanin, Maarten Zwart

The localisation of bicoid and oskar mRNAs to the anterior and posterior poles of the *Drosophila* oocyte defines the AP axis of the embryo, and provides an excellent model for analysing the molecular mechanisms that underlie cell polarity and mRNA localisation. We are taking a combination of cell-biological, genetic and molecular approaches to investigate these mechanisms:

1) The dsRNA-binding protein, Staufen, is required for the microtubule-dependent localisation of bicoid and oskar mRNAs, and for the actin-dependent localisation of prospero mRNA in neuroblasts. We are investigating how Staufen mediates mRNA transport along both actin and microtubules, and are analysing other proteins required for these processes. Since Staufen co-localises with these mRNAs, we are also using GFP-Staufen to visualise mRNA transport *in vivo*.

2) We have shown that the homologues of three genes required for AP axis formation in *C elegans* (PAR-1, LKB1 (PAR-4), and 14-3-3 (PAR-5)) are required for the polarisation of the oocyte. Furthermore, mutants in these genes disrupt epithelial polarity. We are now screening for other components of this conserved polarity pathway, and are analysing how it regulates the cytoskeleton.

3) Since many proteins involved in mRNA transport or cell polarity are required throughout development, they were not identified in the classical screens for mutations that disrupt axis formation. To overcome this problem, we are performing screens in germline clones for mutants that affect GFP-Staufen localisation. We have identified many novel genes required for the polarisation of the oocyte or for the localisation of bicoid or oskar mRNA, and are now analysing their functions.

Inset left: NMR structure of one double-stranded RNA binding domain from Staufen protein (red) bound to a 22bp RNA stem-loop (blue). The amino acid side-chains that contact the RNA are shown in yellow. Collaboration with Andres Ramos and Gabrielle Varani (LMB-MRC).

Palacios I, Gatfield D, St Johnston D and Izaurralde I (2004) An eIF4AIII-containing complex required for mRNA localization and nonsense-mediated mRNA decay. **Nature** 427, 753-757

Huynh JR, Munro T, Smith Litière K and St Johnston D (2004) The Drosophila hnRNPA/B homologue, Hrp48, is specifically required for a distinct step in osk mRNA localisation. **Dev. Cell** 6, 625-635

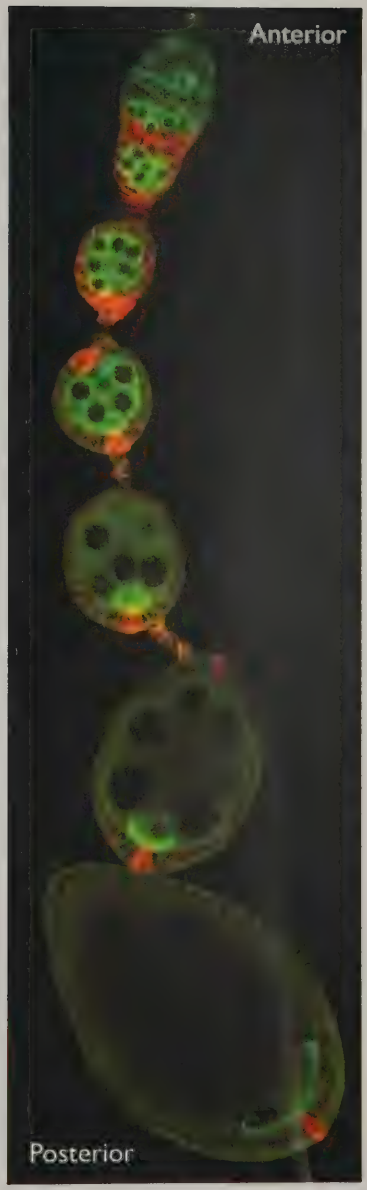
Benton R and St Johnston D (2003) Drosophila PAR-1 and 14-3-3 inhibit Bazooka/PAR-3 to establish complementary cortical domains in polarized cells. **Cell** 115, 691-704

For an additional publication since the last report, see number 78 on pp 55-62

A Drosophila ovariole containing [illegible] progress through oogenesis. [illegible] anterior of the ovariole and become [illegible] as they exit the germarium. Each cyst contains 16 germ cells, and one of these is selected to become the oocyte and accumulates higher levels of BicD protein

Mutants in LKB1 disrupt oskar mRNA localisation and the polarity of the microtubule cytoskeleton. The localisation of GFP-Staufen (green, left), oskar mRNA (centre) and microtubules (right) in wildtype oocytes (top), and in lkb1 mutant germline clones (bottom)

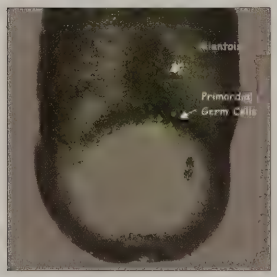
[illegible] bicoid mRNA [illegible] oskar mRNA (red) to the anterior and posterior poles of the stage 9 oocyte



Azim Surani

Germ cells: a genetic programme regulating specification and epigenetic modification

Co-workers: Sheila Barton, Francesca Cesari Weimar, Gabriela Durcova-Hills, Lynn Froggett, Petra Hajkova, Sophie Hanina, Katsuhiko Hayashi, Sean Jeffries, Masahiro Kaneda, Ulrike Lange, Caroline Lee, Bernhard Payer, Fuchou Tang, Wee Wei Tee, Leng Siew Yeap



Germ cells are the source of totipotency, a unique state that links all generations. We are investigating the genetic programme, which regulates specification of founder primordial germ cells (PGCs), and the epigenetic programming of the lineage, which underlie the distinctive properties of mouse germ cell lineage.

A particular focus of our work has been to elucidate the mechanism of PGC specification by using molecular analysis of single founder germ cells and their nearest somatic neighbours. This has led, amongst other things, to the identification of Blimp1, a transcriptional regulator as the key determinant of the mouse germ cell lineage. Blimp1 is first detected in a few pluripotent epiblast cells at E6.25, which marks the emergence of PGC precursors to the 40 or so founder PGCs seen at E7.25. A specific role of Blimp1 is to repress the somatic programme represented by region-specific Hox genes in founder PGCs. PGCs are highly specialised cells, but it is possible to derive pluripotent stem cells from PGCs in culture.

Extensive epigenetic programming of the genome in PGCs follows their specification, which is an essential first step towards eventual totipotency. In particular, when PGCs migrate into developing gonads at E11.5, they undergo substantial epigenetic modifications, including genome-wide DNA demethylation, erasure of imprints and reactivation of the X chromosome. We are investigating the mechanism and identity of the intrinsic factors involved in this event, together with the nature of the external signals that trigger it.

Our broader objectives are to use our comprehensive knowledge of the mechanism of germ cell specification and properties, to elucidate mechanisms of cell fate determination generally, for example, during differentiation of pluripotent embryonic stem cells. Mechanisms that govern erasure of epigenetic information in PGCs could be extended to investigate genomic reprogramming and dedifferentiation of somatic cells when they acquire pluripotency.

Inset left: Expression of stella-GFP at E 7.8. PGCs are detected at the base of the allantois. Stella is located within a cluster of pluripotency genes, including nanog and Gdf3 that are expressed in ES and EG cells.

Surani MA, Ancelin K, Hajkova P, Lange UC, Payer B, Western P and Saitou M (2004) Mechanism of germ cell specification: a genetic programme regulating epigenetic reprogramming. **Cold Spring Harbor Symposium** 69 (Epigenetics), 1-9

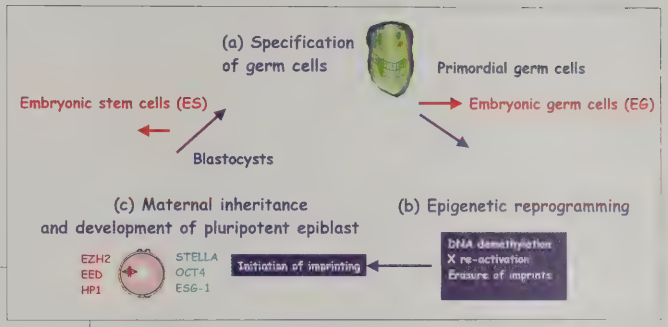
Ohinata Y, Payer B, O'Carroll D, Ancelin K, Ono Y, Sano M, Barton SC, Obukhanych T, Nussenzweig M, Tarakhovsky A, Saitou M, and Surani MA. (2005) Blimp1 is a critical determinant of the germ cell lineage in mice. **Nature** 436, 207-213

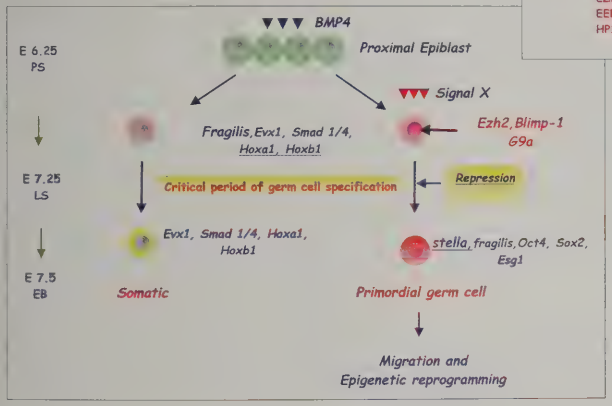
Bao S, Miyoshi N, Okamoto I, Jenuwein T, Heard E and Surani MA (2005) Initiation of epigenetic reprogramming of the X chromosome in somatic nuclei transplanted to a mouse oocyte. **EMBO reports** 6, 748-754

Surani MA (2005) Nuclear reprogramming by human embryonic stem cells. **Cell** 122, 653-654.

For complete list of this lab's publications since the last report, see numbers 10, 19, 21, 58, 68, 69, 80 & 86 on pp 55-62

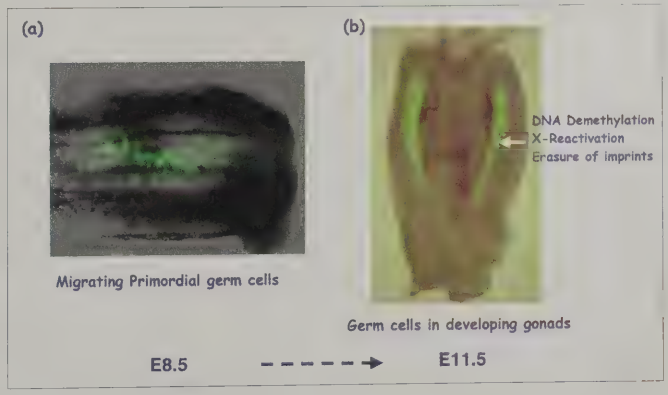
Mouse germ line cycle. (a) Founder population of primordial germ cells are detected at E7.5 consisting of about 45 cells. (b) They proliferate and migrate into the developing gonads at E10.5, when a major epigenetic reprogramming event commences, and continues during gametogenesis. (c) There is also maternal inheritance of key epigenetic and totipotency factors in oocytes, which are essential for early development.





Mechanism of PGC specification. The proximal epiblast cells acquire germ cell competence in response to signalling molecules, including BMP4. Some of these cells acquire PGC fate subsequently, which is associated with transcriptional repression of genes that are expressed in the neighbouring cells, including Hox genes. Several epigenetic modifiers including Ezh2, G9a and Blimp 1 probably have a critical role in the process. PGCs express pluripotent-specific genes such as Oct4, and the germ cell specific gene, stella, which is the definitive marker of nascent PGCs.

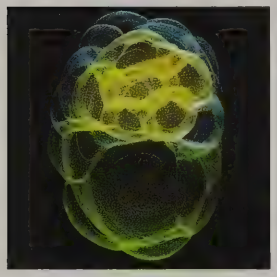
Epigenetic reprogramming in PGCs. (a) PGCs expressing Stella-GFP are seen migrating into the developing gonads. (b) When PGCs enter into the developing gonads, they undergo extensive epigenetic reprogramming of the genome that includes genome-wide DNA demethylation and reactivation of the inactive X-chromosome.



Magdalena Zernicka-Goetz

Development of spatial patterning and cell fate in the early mouse embryo

Co-workers: Dilly Bradford, Joanna Grabarek, Seiki Haraguchi, Tagbo Ilozue, Karin Lykke-Andersen, Sigolene Meilhac, Emlyn Parfitt, Berenika Plusa, Lucy Richardson, Maria-Elena Torres-Padilla



We are interested in origins of spatial patterning and cell fate determination in the mouse embryo focusing on three major questions.

First, how is the polarity of the egg first established to permit the drastically asymmetric, meiotic divisions and then re-organised following fertilisation to allow apparently symmetric, embryonic divisions? We are addressing this question by a combination of experimental embryology and molecular techniques to disturb egg polarity. Time-lapse fluorescent imaging allows us to follow dynamics of these processes and the ectopic expression of GFP-fusion proteins enables us to perturb these processes.

Second, how are the decisions made to allow early embryonic cells to shift their division patterns from being initially symmetric to asymmetric in order to establish inside and outside cells with different potency and thereby a different fate? We have recently found that we can change these cell fate decisions by down-regulating the function of cellular polarity proteins such as Par3 and aPKC. This leads us to study the role of these proteins and their partners in establishing cellular polarity and cell fate in the early mouse embryo. One of our ways to achieve this is by microinjecting dsRNA into individual blastomeres in order to follow the consequences in a clonal population of cells.

Third, we would like to understand further the influence of these asymmetric events in the preimplantation embryo on the development of first signalling centres important for establishing the anterior-posterior axis. To address when and how are such signalling centers established, we are taking a variety of approaches such as expression profiling and lineage tracing combined with RNAi and overexpression of signalling genes. To determine when and where signalling centres first become active our approach is to transplant them to ectopic sites. Our understanding of these events could be broadened by better knowledge of the spatial and temporal pattern of gene expression when the signalling centres emerge. Thus we have carried out screens that identified novel genes asymmetrically expressed at these early stages and are currently characterising their function.

Inset left: 3D reconstruction of the mouse blastocyst inner cells (yellow: polar trophectoderm blue; mural trophectoderm green.

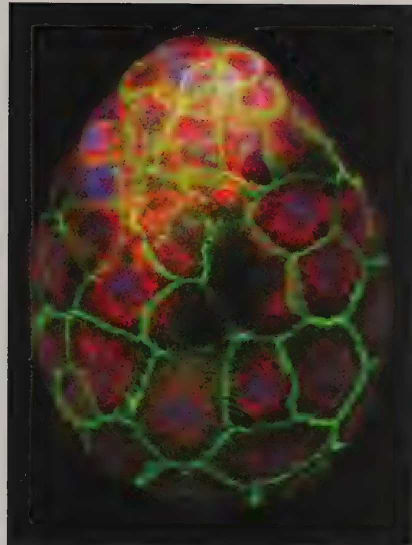
Zernicka-Goetz M (2005) Cleavage pattern and emerging asymmetry of the mouse embryo. **Nature Reviews** 6, 919-928

Plusa B, Hadjantonakis AK, Gray D, Piotrowska-Nitsche K, Jedrusik A, Papaioannou VE, Glover DM, Zernicka-Goetz M (2005) The first cleavage of the mouse zygote predicts the blastocyst axis. **Nature** 434, 391-5

Piotrowska-Nitsche K, Perea-Gomez A, Haraguchi S and Zernicka-Goetz M (2005) 4-cell stage mouse blastomeres have different developmental properties. **Development** 132, 479-490

Plusa B, Frankenberg S, Chalmers A, Hadjantonakis AK, Moore, CA, Papalopulu, N, Papaioannou VE, Glover DM, Zernicka-Goetz M (2005) Downregulation of Par3 and aPKC function directs cells towards the ICM in the preimplantation mouse embryo. **J Cell Sci** 118, 505-515

For complete list of this lab's publications since the last report, see numbers 52, 60, 61, 62, 63, 68 & 88 on pp 55-62



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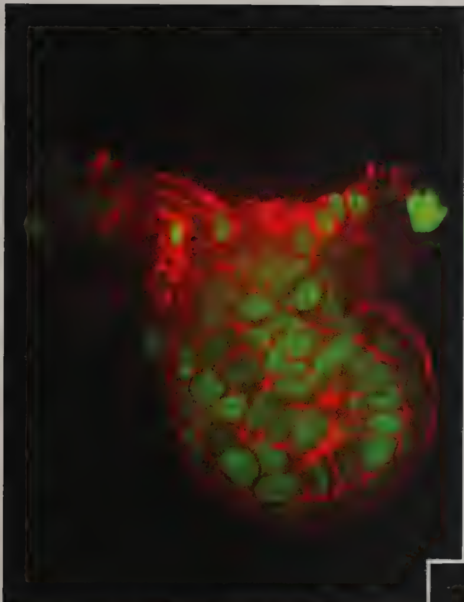
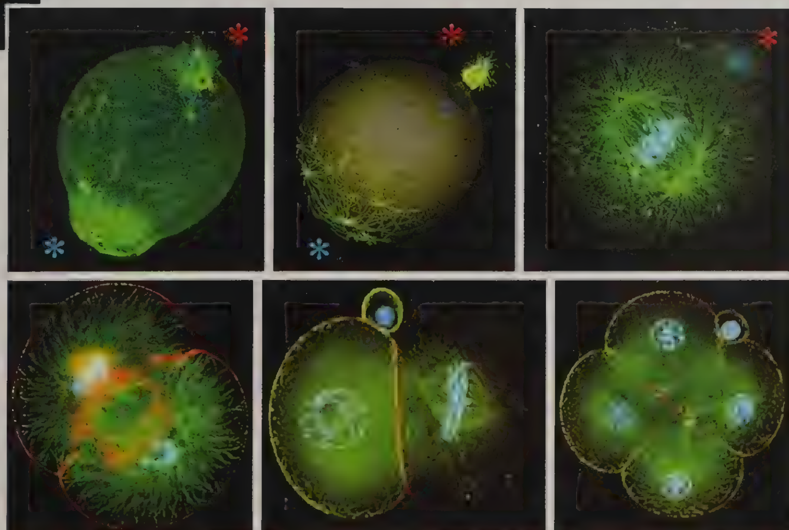


Mouse embryo after implantation (E4.5) - [illegible] of extra embryonic ectoderm [illegible] actin in red [illegible] green. [illegible]



[illegible] Microtubules (green), actin (red), chromatin [illegible]. Blue star sperm entry position. Red star [illegible] of the [illegible]

CATEGORIES OF APPOINTMENT

SENIOR GROUP LEADER
Professor, Reader or equivalent

GROUP LEADER
5-year grant-funded appointment (maximum 10 years)

CAREER DEVELOPMENT FELLOW
4-year grant-funded appointment, within individual groups

INDEPENDENT SENIOR RESEARCH ASSOCIATE
3-year grant-funded appointment, within individual groups

RESEARCH ASSOCIATE/FELLOW
Postdoctoral Fellow, within individual groups, appointed by group leader

RESEARCH ASSISTANT
Postgraduate, within individual groups, mainly grant-funded

GRADUATE STUDENT
3-year studentship within individual groups, mainly grant-funded

RESEARCH TECHNICIAN
Within individual groups, mainly grant-funded

LABORATORY ASSISTANT
Within individual groups or part of core support, grant-funded

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As part of the University of Cambridge, the Institute welcomes enquiries from prospective graduate students. We have a thriving population of graduates who contribute greatly, not only to the stimulating research environment, but also to the life of the Institute as a whole. Additionally, graduates become members of the biological or medical sciences department to which their group is affiliated. Graduate studentships are supported mainly by the Wellcome Trust or Cancer Research UK but additional sponsorship may be solicited from a variety of sources, including government research councils. Applicants should write, in the first instance, to the leader of the group they wish to join.

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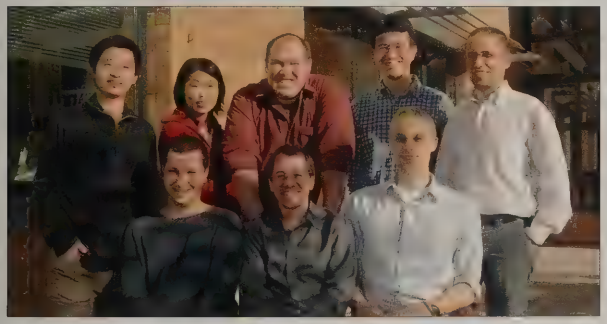

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GILLIAN HYNES
URSZULA KOKOT
KATARZYNA NOWAK
ROBIN PLUMRIDGE
DAVID SIMPSON
HILARY WOODCOCK

CATERING

ROB O'DONNELL
DARIA SKRODZKA

The following is a list of articles by members of the Institute that were either published or accepted for publication, since the date of publication of the last Annual Report. (note: refs no 24 and 45 were published prior to 2005, but previously unlisted in Institute reports).

* Indicates equal priority.

1 Abbott AL*, Alvarez-Saavedra E*, Miska EA*, Lau NC, Bartel DP, Horvitz HR, Ambros V (2005) The let-7 microRNA family members mir-48, mir-84, and mir-241 function together to regulate developmental timing in *Caenorhabditis elegans*. **Dev Cell** 9, 403-414

2 Ahringer J ed. (2006) Reverse genetics, *WormBook*, ed. The *C elegans* Research Community. **WormBook** doi/10.1895/wormbook.1.47.1 http://www.wormbook.org

3 Ahringer J (2005) Playing ping pong with pins: cortical and microtubule-induced polarity. **Cell** 123, 10-12

4 Alvarez-Garcia I, Miska EA (2005) MicroRNA functions in animal development and human disease. **Development** 132, 4653-4662

5 Alvarez-Saavedra EA, Miska EA (2005) *Caenorhabditis elegans* and friends in Los Angeles. **Genome Biology** 6, 358

6 Amaya E (2005) Xenomics. **Genome Research** 15, 1683-1691

7 Bannister AJ, Schneider R, Myers FA, Thorne AW, Crane-Robinson C and Kouzarides T (2005) Spatial distribution of di-and tri-methyl lysine 36 of histone H3 at active genes. **J Biol Chem** 280, 1772-1773

8 Bannister AJ and Kouzarides T (2005) Reversing histone methylation. **Nature** 436, 1103-1106

9 Bannister AJ and Kouzarides T (2005) Differentiation and gene regulation. **Curr Opin Genet Development** 15, 473-5

10 Bao S, Miyoshi N, Okamoto I, Jenuwein T, Heard E and Surani MA (2005) Initiation of epigenetic reprogramming of the X chromosome in somatic nuclei transplanted to a mouse oocyte. **EMBO Reports** 6, 748-754

2x fixed *C.elegans* embryos engulfed in maternal tissue, stained with an anti tubulin ant body, (green), an anti PAR-2(red) and DAPI showing the DNA (blue). Nathalie LeBot (2005)

11 Barros T, Kinoshita K, Hyman, AA, and Raff JW (2005) Aurora-A activates D-TACC/Msps complexes exclusively at centrosomes to stabilise centrosomal Mts. **J Cell Biol** 170, 1039-1046

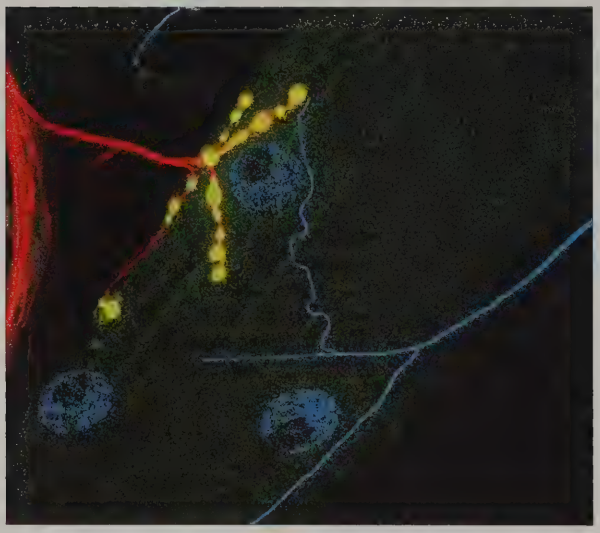
12 Bécam IE, Tanentzapf G, Lepesant J-A, Brown NH and Huynh J-R (2005) Integrin-independent repression of cadherin transcription by talin during axis formation in *Drosophila*. **Nat Cell Biol** 7, 510-516

13 Birsoy B, Berg LB, Williams PH, Smith JC, Wylie CC, Christian JL and Heasman J (2005) XPACE4 is a localized proprotein convertase required for mesoderm induction and the cleavage of specific TGF-β proteins in *Xenopus* development. **Development** 132, 591-602

14 Brand AH and Livesey FJ (2005) Cell Differentiation. **Curr Opin Cell Biol**, 17 (6), 637-638

15 Brown DD, Shauna N, Martz SN., Binder O, Price BMJ, Smith JC and Conlon FL (2005) Tbx5 and Tbx20 act synergistically to control vertebrate heart morphogenesis. **Development** 132, 553-563

16 Callery EM, Smith JC and Thomsen GH (2005) The ARID domain protein dril1 is necessary for TGFβ signaling in *Xenopus* embryos. **Dev Biol** 278, 542-559



A synapse between a *Drosophila* neuron and its target muscle (anti-synaptotagmin, green; anti-HRP, red; nuclei stained with DAPI, blue; trachae, blue). (Ugo Mayor, 2005)

17 Chavali GB, Ekblad CM, Basu BP, Brissett NC, Veprintsev D, Hughes-Davies L, Kouzarides T, Itzhaki LS, Doherty AJ (2005) Crystal structure of ENT domain of human EMSY. **J Mol Biol** 350, 964-973

18 Chodagam S, Royou A, Whitfield W, Karess R and Raff JW (2005) The centrosomal protein CP190 regulates myosin function during early *Drosophila* development. **Curr Biol** 15, 1308-1313

19 Chuva de Sousa Lopes SM, van den Driesche S, Carvalho RL, Larsson J, Eggen B, Surani MA and Mummery CL (2005) Altered primordial germ cell migration in the absence of transforming growth factor beta signaling via ALK5. **Dev Biol** 284, 194-203

20 Collart C, Verschueren K, Rana A, Smith JC and Huylebroeck D (2005) The novel Smad-interacting protein SmicI regulates *Chordin* expression in the *Xenopus* embryo. **Development** 132 4575-4586

21 Curley JP, Pinnock SB, Dickson SL, Thresher R, Miyoshi N, Surani MA and Keverne EB (2005) Increased body fat in mice with a targeted mutation of the paternally expressed imprinted gene Peg3. **FASEB J** 19, 1302-4

22 Dawes-Hoang RE, Parmar KM, Christiansen AE, Phelps CB, Brand AH and Wieschaus EF (2005) Folded gastrulation, cell shape change and the control of myosin localization. **Development** 132, 4165-4178.

23 Downs JA, Allard S, Jobin-Robitaille O, Javaheri A, Auger A, Bouchard N, Kron SJ, Jackson SP, and Cote J (2004) Binding of chromatin-modifying activities to phosphorylated histone H2A at DNA damage sites. **Molecular Cell** 16, 979-90

Sensory rays of the *C.elegans* male tail. (David Welchman, 2005)

24 Durcova-Hills, G and McLaren A (2004) Isolation and maintenance of murine embryonic germ cell lines. In: **Handbook of Stem Cells** Vol 1 Ed. Robert Lanza et al. Academic Press

25 Egger B, Chell J and Brand AH (2006) *Drosophila* Neurogenesis. In: **Stem Cells and Brain Repair**. Eds Theo Palmer et al. Philosophical Transactions B, Biological Sciences [in press]

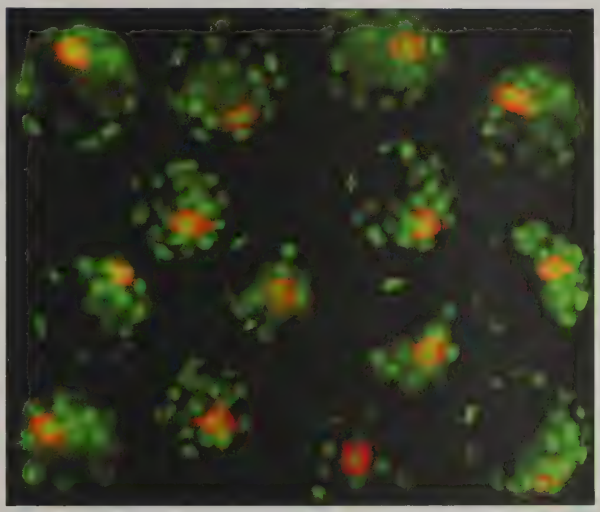
26 Ekblad CM, Chavali GB, Basu BP, Brissett NC, Veprintsev D, Hughes-Davies L, Kouzarides T, Donherty AJ and Itzhaki LS (2005) Binding of EMSY to HP1beta implications for recruitment of HP1beta and BS69. **EMBO Rep** 6, 675-680

27 Falck J, Coates J and Jackson SP (2005) Conserved modes of recruitment of ATM ATR and DNA-PKcs to sites of DNA damage. **Nature** 434, 605-611

Professor Sir John Gurdon, sitting on the shoulders of giants at the Institute Annual Retreat, Lad. Margaret Hall, Oxford (John Overton, 2005)

28 Farmer H, McCabe N, Lord CJ, Tutt ANJ, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Martin NMB, Jackson SP, Smith GCM and Ashworth A (2005) Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. **Nature** 434, 917-921

29 Gurdon JB, Byrne JA and Simonsson S (2005) Nuclear reprogramming by *Xenopus* oocytes. From: **2005 Stem cells: nuclear reprogramming and therapeutic applications**. Wiley, Chichester, Novartis Foundation Symposium, 265, 129-141



Living mouse embryos from an histone-GFP line cont[illegible] with a membrane-RFP. (Sigolene Meilhac, 2005)

30 Gurdon JB (2005) The conservation of the genome and nuclear reprogramming in *Xenopus*. In: Section IX: Vertebrate Cloning. From: **Key experiments in practical developmental biology**, 310-315. Ed. M Marr-Beffa, J Knight, Cambridge University Press

31 Gurdon JB (2005) Amphibian nuclear transfer and future directions of research. In: **Health Consequences of cloning**, 29-32. Ed A Inui, CRC Press LLC, USA.

32 Gurdon JB (2005) Reproductive cloning: past, present and future. Reproductive BioMedicine Online 10, Suppl 1, 43-44 and Discussion: 56-59. **Ethics, Law and Moral Philosophy of Reproductive Biomedicine** Conference, Royal Society, London.

33 Gurdon JB (2005) The use of *Xenopus* oocytes and embryos as a route towards cell replacement. **J Bioscience** 30, 11-14.

34 Gurdon JB (2005) Sinistral snails and gentlemen scientists. **Cell** 123, 751-753

35 Guse A, Mishima M, Glotzer M (2005) Phosphorylation of ZEN-4/MKLP1 by aurora B regulates completion of cytokinesis. **Curr Biol** 15, 778

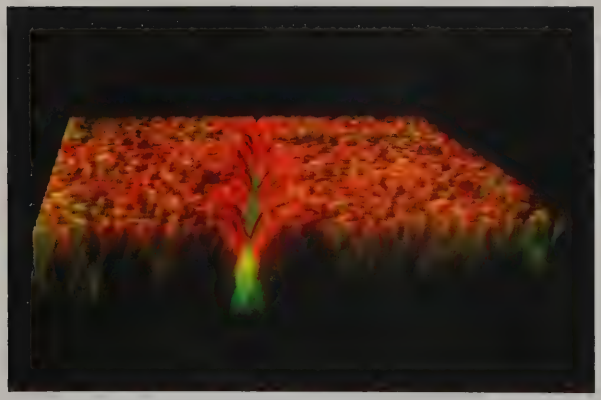
36 Harmer NJ, Sivak J, Amaya E and Blundell TL (2005) 1.15 Å crystal structure of the *X tropicalis* Spred1 enabled/vasodilator-stimulated phosphoprotein homology-1 domain. **FEBS Letters** 579,1161-1166

37 Harvey AC, Jackson SP and Downs JA (2005) *Saccharomyces cerevisiae* histone H2A Ser122 facilitates DNA repair. **Genetics** 170, 543-553

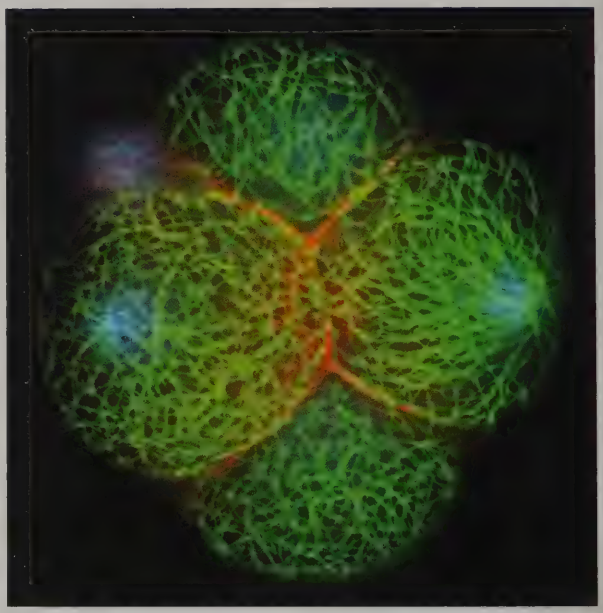
38 Hizlan D, Mishima M, Tittmann P, Gross H, Glotzer M, Hoenger A (2006) A structural analysis of the ZEN-4/CeMKLP1 motor domain and its interaction with microtubules. **J Struct Biol** 153, 73-84

39 Jazayeri A, Falck J, Lukas C, Bartek J, Lukas J, Smith GCM and Jackson SP (2006) ATM and cell cycle-dependent regulation of ATR in response to DNA double-strand breaks. **Nat Cell Biol** 8, 37-45

40 Jullien J and Gurdon J. (2005) Morphogen gradient interpretation by a regulated trafficking step during ligand-receptor transduction. **Genes & Development** 19, 2682-2694



3D reconstruction of midline cells (green) segregating from the ectoderm (red) to join the developing CNS. (Torsten Bossing 2005)



4-cell stage mouse embryo. Microtubules in green (Berenika Plusa, 2004)

41 Kinoshita K, Noetzel TL, Pelletier L, Mechtler K, Drechsel DN, Schwater A, Lee M, Raff JW and Hyman AA (2005) Aurora A phosphorylation of TACC3/Maskin is required for centrosome dependent microtubule assembly in mitosis. **J Cell Biol** 170, 1047-1055

42 Lau A, Swinbank KM, Ahmed PS, Taylor DL, Jackson SP, Smith GCM and O'Connor MJ (2005) Suppression of HIV-1 infection by a small molecule inhibitor of the ATM kinase. **Nat Cell Biol** 7, 5, 493-500

43 Lee AC Fernandez-Capetillo O, Pisupati V, Jackson SP and Nussenzweig A (2005) Specific association of mouse MDC1/NFBD1 with NBS1 at sites of DNA- damage. **Cell Cycle** 4, 177-182

44 Lu J*, Getz G*, Miska EA*, Alvarez-Saavedra E, Lamb J, Peck D, Sweet-Cordero A, Ebert BL, Mak RH, Ferrando AA, Downing JR, Jacks T, Horvitz HR, Golub TR (2005) MicroRNA expression profiles classify human cancers. **Nature** 435, 834

45 McLaren, A. (2002) Cloning: Pathways to a Pluripotent Future. In **Science Pathways of Discovery** Amato I (Ed) John Wiley.

46 McLaren, A (2004) Primordial germ cells in mouse and human. In: **Handbook of Stem Cells**, Vol 1. Ed. Robert Lanza et al. Academic Press

47 McLaren A (2005) Cloning mammals: a good look at the biology. **BioEssays** 27, 229

48 McLaren A and Lawson KA (2005) How is the mouse germ-cell lineage established? **Differentiation** 73, 1-3

49 McLaren A (2005) Chapters 13 and 39 (with G. Durcova-Hills) In: **Essentials of Stem Cell Biology.** Ed. R. Lanza, Elsevier-Academic Press

Alison Rule, Professor Steve Jackson and Chloe Higgins (CR-UK) raising [illegible] Cancer awareness on behalf of Cancer Research UK. Roger Adams, 2005

Cytoskeleton (green), and DNA (blue) of a [illegible] 2005)

50 Messenger NJ, Kabitschke C, Andrews R, Grimmer D, Nuñez Miguel R, Blundell T L, Smith J C and Wardle F C (2005) Functional specificity of the *Xenopus* T-domain protein Brachyury is conferred by its ability to interact with Smad1. **Dev Cell** 8, 599-610

51 Miska EA (2005) How microRNAs control cell division, differentiation and death. **Curr Opin Genet Dev** 15, 563-568

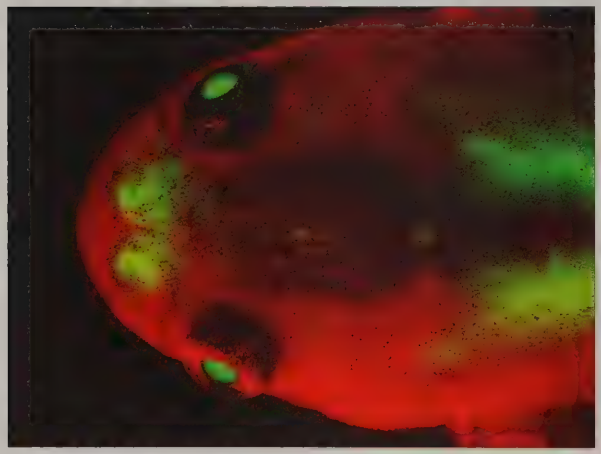
52 Moore CA, Zernicka-Goetz M (2005) PAR1 and the microtubule-associated proteins CLASP2 and dynactin-p50 have specific localisation on mouse meiotic and first mitotic spindles. **Reproduction** 130, 311-320

53 Moumen A, Masterson P, O'Connor M and Jackson SP (2005) HnRNP K: An HDM2 target and transcriptional co-activator of p53 in response to DNA damage. **Cell** 123, 1065-1078

54 Narasimha M and Brown NH (2005) Integrins and associated

proteins in *Drosophila* development. In **Integrins and Development**. Ed. E Danen, Landes Bioscience

55 Narasimha M. and Brown NH (2005) Confocal microscopy of *Drosophila* embryos. In **Cell Biology: a Laboratory Manual**, 3rd edition Ed. J de Celis, Academic Press



Double transgenic frog using Pax6 promoter driven GFP in central nervous system and CMV promoter driven RFP ubiquitously. (Jun-An Chen, 2005)

56 Ng RK and Gurdon JB (2005) Epigenetic memory of active gene transcription is inherited through somatic cell nuclear transfer. **PNAS** 102, 1957-1962

57 Ng RK and Gurdon JB (2005) Maintenance of epigenetic memory in cloned embryos. **Cell Cycle** 4, e110-e113.

58 Ohinata Y, Payer B, O'Carroll D, Ancelin K, Ono Y, Sano M, Barton SC, Obukhanych T, Nussenzweig M, Tarakhovsky A, Saitou M, Surani MA (2005) Blimp1 is a critical determinant of the germ cell lineage in mice. **Nature** 436, 207-213.

59 Pines J and Lindon C (2005) Proteolysis: anytime, any place, anywhere? **Nat Cell Biol** 7, 731-735

60 Piotrowska-Nitsche K, Perea-Gomez A, Haraguchi S and Zernicka-Goetz M (2005) Four-cell stage mouse blastomeres have different developmental properties. **Development** 132, 479 - 490

61 Piotrowska-Nitsche K and Zernicka-Goetz M (2005) Spatial arrangement of individual 4-cell stage blastomeres and the order in which they are generated correlate with blastocyst pattern in the mouse embryo. **Mech Dev** 122, 487-500

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Professor Jim Smith addressing the Institute's Opening Symposium in June. (John Overton, 2005)

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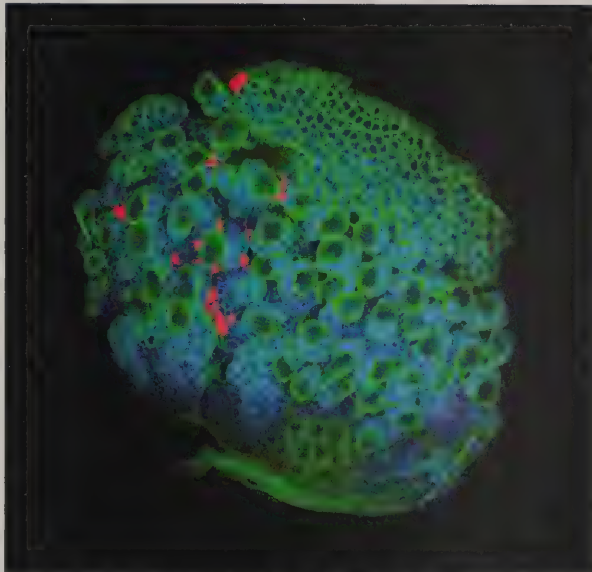

Large neural stem cells of the [illegible] DAPI in blue, histone RFP [illegible] Patched GAL4 [illegible] Chell, 2005)

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HONOURS AND AWARDS

ANDREA BRAND - Joint Winner of the William Bate Hardy Prize

JOHN GURDON - Charles M and Martha Hitchcock Professorship at the University of California, Berkeley, 2005-2006.

ANNE McLAREN - Appointed The Raman Professor for 2005 by the Indian Academy of Sciences.

JON PINES - Elected Fellow of the Academy of Medical Sciences.

DANIEL ST JOHNSTON - Elected Fellow of the Royal Society and the Academy of Medical Sciences

AZIM SURANI - Appointed Sir Dorabji Tata Professor, Tata Institute for Fundamental Research, NCBS, Bangalore, India, 2005-2010.

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JANA VOIGT left to take up a new position in Brussels with the European Commission

ADAM WALKER took up a new position at Domantis

XIAO-YIN ZHANG started a PhD course at the MRC Laboratory of Molecular Biology

Renata Basto (Raff Lab), winner of this year's Annual Report Cover Competition, enlisting some help for next year's entry. (John Overton, 2005)

ACKNOWLEDGEMENTS

Prospectus produced in the Wellcome Trust/Cancer Research UK Gurdon Institute. Edited by Ann Cartwright, production by Alastair Downie.

Group photographs by Chris Green (Dept of Biochemistry)

Printed by Cambridge Printing, the printing business of Cambridge University Press www.cambridgeprinting.org

Front cover: Wild-type *Drosophila* sperm elongation. The nuclei are seen in blue (dapi staining), mitocondria autofluorescense in green and basal bodies (red) are detected with γ-tubulin antibody (Renata Basto, 2005)

Back cover: Images from the Gurdon Institute Opening Symposium, June 2005 (John Overton)

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